DIMETHYLAMINOPHENYL AND CYCLOPROPYL SUBSTITUTED ANTHRACENES AND BENZ[a]ANTHRACENES

by

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THIS THESIS IS MOST AFFECTIONATELY DEDICATED TO

MY WIFE AND PARENTS

ACKNOWLEDGMENTS

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INTRODUCTION

INTRODUCTION

One of the dreams of science had long been that substances would be found that would attack disease-producing agents in the body without doing damage to the body itself. By means of his studies on the curative effect of arsenic compounds in the treatment of syphilis, Paul Ehrlich proved in 1909 that perhaps this was not just a dream.[1] Since the advent of Ehrlich's "magic bullet", chemotherapy has advanced from the use of very crude remedies to the hormones and antimetabolites of today. The word chemotherapy, coined by Ehrlich,[2] has become familiar to the majority of the population due to the extensive publicity given in recent years to cancer chemotherapy.

Cancer is nothing new to mankind. It was described in medical writings as early as 1500 B. C., as noted in the famous Ebers papyrus.[3] In 1875 Volkmann recognized that there was a causal connection between skin tumors of workers in the tar industry and the tar itself.[4] The work of the British investigators, Cook and Kennaway, has been exhaustively reviewed.[5] From these beginning researches on chemical carcinogenesis ultimately evolved the beginning of cancer chemotherapy.

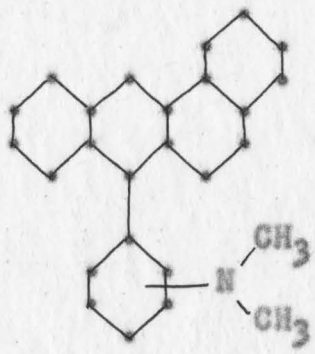
Research on chemical carcinogenesis led to the discovery and eventual synthesis of carcinostats and carcinolytes.* At present the United States Federal Government has initiated a crash program, not unlike the war-time search for antimalarials, to screen compounds to find effective carcinolytes. The problem has been that the exact nature and causes of cancer have not been found. A concerted effort is being made to correlate anti-cancer activity with chemical structure.[6] From these structure-activity correlations limited deductions can be made concerning the mechanism of action of some of the compounds. At the same time specific aspects of structure can be noted and used in attempted synthesis of "tailor-made" anti-cancer agents.

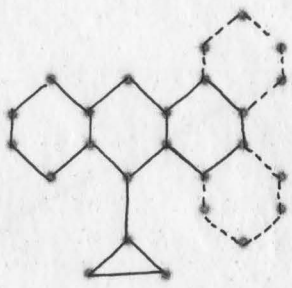
It is the purpose of this dissertation to investigate the reactions leading to certain polynuclear compounds containing some of the structural systems which have been shown to have

---

* In current chemical and biological literature a wide variety of terms are used to designate an anti-tumor agent. A carcinostat is an agent which will halt the growth of a cancerous tumor, while a carcinolyte is an agent which will actually cause a gradual destruction of the abnormal growth. Unfortunately both terms are often used interchangeably.

carcinolytic properties. With this in mind this author decided to attempt to prepare the following series:





These two series shown above contain the phenylbenz[a]anthracene system, the dimethylamino group and/or the cyclopropane system, all of which have demonstrated anti-tumor activity in certain compounds. This activity will be discussed in detail in the following section.

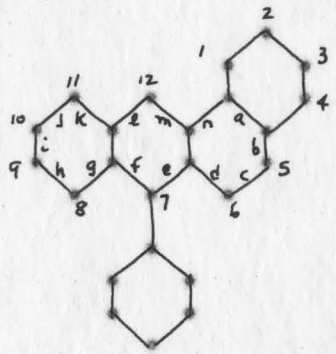
These syntheses, as well as the results and conclusions will be discussed in detail in the following sections of this thesis. The author feels that this work will not only contribute to the cancer research effort, but at the same time, through studies of the unique chemical properties and mode of synthesis of these products and their precursors, make a definite contribution to the advancement of the field or organic chemistry.

NOMENCLATURE

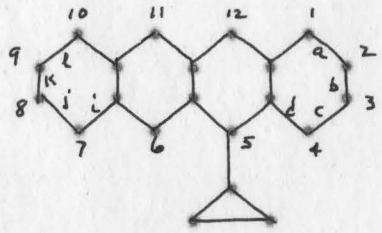
NOMENCLATURE

The nomenclature used throughout this thesis is in accordance with that suggested in "Definitive Rules for Nomenclature of Organic Chemistry," J. Am. Chem. Soc., 82, 5545 (1960).

Examples are as follows:



7-Phenylbenz[a]anthracene



5-Cyclopropylnaphthacene

All six-membered rings throughout this thesis are fully aromatic unless otherwise noted. All three-membered rings illustrated are completely saturated

unless otherwise noted. No attempt has been made to depict structures in their three-dimensional conformations. It should be understood that in the above examples the substituent rings do not lie in the same plane as the polynuclear ring system.

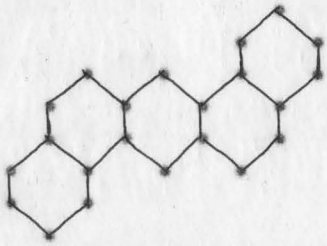
HISTORICAL

HISTORICAL

A. Carcinogen and Carcinolyte

Chemical carcinogenesis, which was first demonstrated by Yamagiwa and Ichikawa[7] in 1915, became one of the most active lines in cancer research after 1932 when Cook and his associates[8,9] produced cancer in mice by the application of pure synthetic substances. The first pure carcinogenic compound, dibenz[a,h]anthracene (1), was synthesized independently by Clar[10] and Kennaway.[11]

Of the hundreds of polycyclic hydrocarbons that have since been tested for carcinogenic power, only one, benzo[a]pyrene (2), has been isolated from tar,[5] the first proved source of cancer-producing agents.[7]



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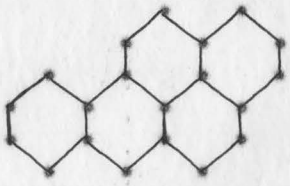

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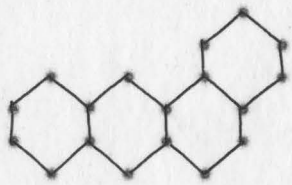
The yield of benzo[a]pyrene from tar was minute; Hieger[12] isolated only fifty grams of it from two tons of pitch.

The classic work of Cook and Kennaway[13] on carcinogens demonstrated the presence of the benz[a]anthracene (3) ring system, with substutents at either the 7,8,9- or 12-positions, in the more potent carcinogenic compounds. This increase of carcinogenicity of 7- and 12-methylbenz[a]anthracene



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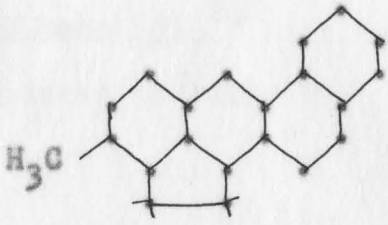
may be interpreted as an electronic effect[14] due to the introduction of the alkyl substituent into the meso positions. Jones[15] has shown that such meso substitution in benz[a]anthracene causes the largest bathochromic shift in the ultraviolet absorption maxima. However, Yang[16] believes that besides the electronic factors there is a steric factor responsible for the carcinogenicity of the polynuclear aromatic hydrocarbon.

To be carcinogenic it must bear steric resemblance to an active steroid. Yang has shown that among polynuclear aromatic hydrocarbons of similar electronic properties, the closer the steric resemblance to a steroid the higher the carcinogenicity. Thus, carcinogenesis by these hydrocarbons may be the result of their interference with normal steroid activity. This hypothesis is supported by the biological observations of Baserga and Shubik.[17] Furthermore, the most potent polynuclear aromatic hydrocarbon known today, 3-methylcholanthrene,[18] can be easily recognized as a 7,8,9-substituted benz[a]anthracene (4) or as a dehydrogenated steroidal derivative (5).



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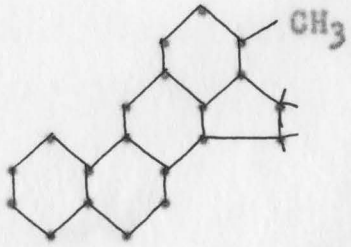

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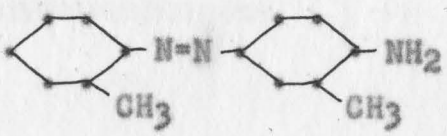
Of the carcinogenic substances outside the class of polycyclic hydrocarbons those of the azo dye group are the most important. Two of these, o-amino-azotoluene (6),[19] and p-dimethylaminoazobenzene (7)[20]

readily produce liver cancer in rats. Pullman[21,22] has shown that while p-aminoazobenzene is non-carcinogenic, the mono-N-methyl derivative is slightly carcinogenic and



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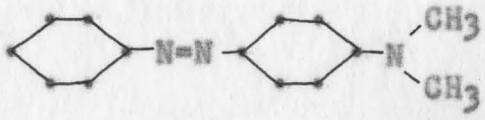

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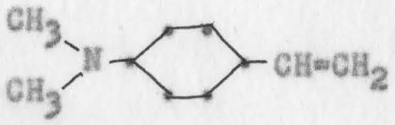
the dimethylamino derivative 7 is a potent carcinogen. Miller[23] reports that an unsubstituted 2-position in derivatives of 7 is necessary for carcinogenic effect on rat liver.

Carcinoma of the auditory duct of the ear of rats is caused by oral administration of 4-dimethylamino-stilbene (8).[24] Mammary and liver cancer have been produced in rats by 2-dimethylaminofluorene (9).[25]



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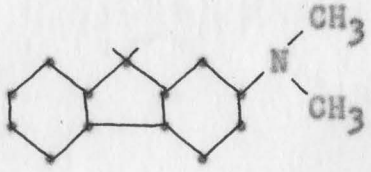

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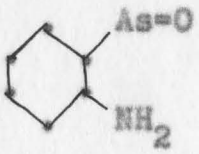
A close correlation of structure has been shown to exist between carcinogens and carcinolytes. The hydrochloride salt of 8 has been shown to exert

powerful inhibition of tumor growth.[26] It has been reported that o-aminoarsenosobenzene (10) drastically increases the ability of x-rays to kill cancer.[27] It is believed by these investigators that o-aminoarsenosobenzene (10) acts as an antisulfhydryl agent



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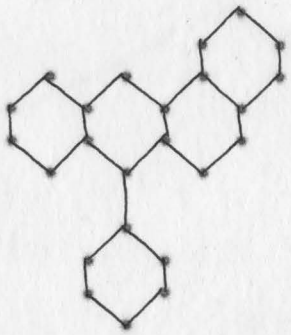

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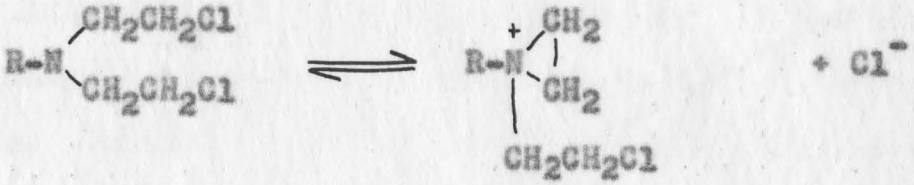
effectively reducing the body's natural defenses against radiation by reacting with such sulfhydryl compounds as cysteine and glutathione which cause the radiation protection. Bond[28] has pointed out that a compound acting as a carcinolyte in one concentration may, in a different concentration or dosage, act as a carcinogen. 7-Phenylbenz[a]anthracene (11), first prepared in This Laboratory,[29] has exhibited carcinolytic potency.[30]

Cancer chemotherapy as we know it today gained impetus from the discovery of the anti-leukemic properties of the nitrogen mustards.[31] It is

generally considered that the nitrogen mustards owe their anti-tumor activity to their ability to cyclize to the highly reactive ethylenimonium ion (13) in polar solvents.[32] Nitrogen mustards have been shown to



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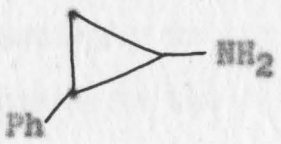
react with such functional groups as amino, sulfhydryl, phosphate and carboxylic acid groups and also water.[33]

The similarity in structure and reactivity of the ethylenimonium ion (14) and cyclopropyl derivatives (15) suggests the possibility of similar physiological

14 15

activity. Indeed various cyclopropane derivatives have exhibited striking physiological effects. Burger[34] has shown that both 2-phenylcyclopropylamine (16) and 1-methyl-2-phenylcyclopropylamine (17) are potent monoamine oxidase inhibitors *in vivo* and *in vitro*.



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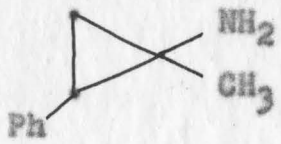

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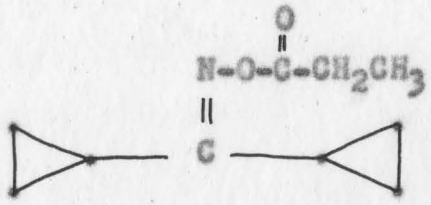
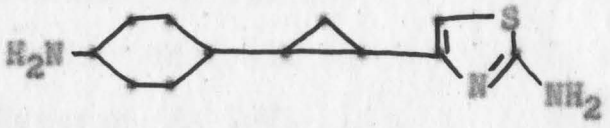
It is interesting to note that Kreutzberg[35] has found unusually large amounts of monoamine oxidase in brain tumors. Belleau and Moran[36] link the enzyme inhibitory action of these two compounds to their sp^2-bond character,[37] a feature characteristic of the transition state for enzymatic oxidation, thereby interfering with normal oxidation. Leiter[38] reported that O-propionyldicyclopropyl ketoxime (18) is moderately effective in the treatment of sarcomas, carcinomas and leukemias.



18

The cyclopropane ring system is present in many pharmacological agents besides those of anti-tumor activity. Burger[39] reported the presence of the cyclopropyl group in an effective tuberculostat, 19. The cyclopropyl group has been shown to be essential

for activity in a new drug, 20, used to produce clinical psychoses in the treatment of mental illness.[40,41]



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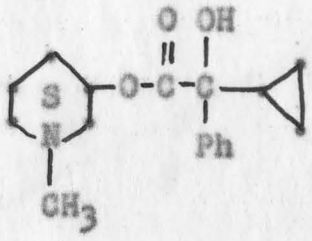

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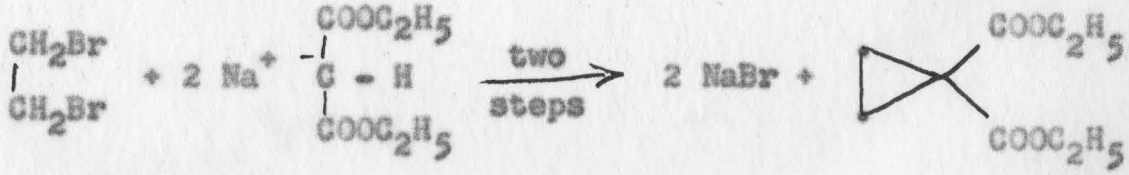
With the indications of activity of the dimethylamino group and the cyclopropyl group a logical extension to the search for carcinolytes would be to prepare and test the dimethylamino derivatives of the known[30] carcinolyte, 7-phenylbenz[a]anthracene (11), and the 7- and 12-cyclopropyl derivatives of benz[a]anthracene.

B. Cyclopropane

In 1876 Victor Meyer[42] stated that a three-carbon ring was incapable of formation and that there was no evidence to warrant the supposition that other rings smaller than six were ever likely to be obtained. However, in 1883 William Perkin, Jr. synthesized diethylcyclobutane-1,1-dicarboxylate from trimethylene dibromide and malonic ester,[43] and later in the same year he synthesized diethylcyclopropane-1,1-dicarboxylate (22) from ethylene dibromide (21) and malonic ester.[44] The synthesis of cyclopropane and cyclobutane derivatives by Perkin gave Baeyer his limited but invaluable experimental data for his classical strain theory in 1885.[45,46]



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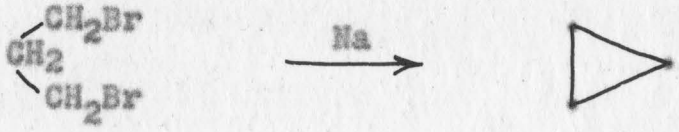
Although Perkin prepared the first pure sample of a cyclopropane derivative, impure cyclopropane (24) was first prepared by Freund[47] in 1882 by using an intramolecular reaction of the Wurtz type on 1,3-dibromopropane (23). This method was greatly improved by



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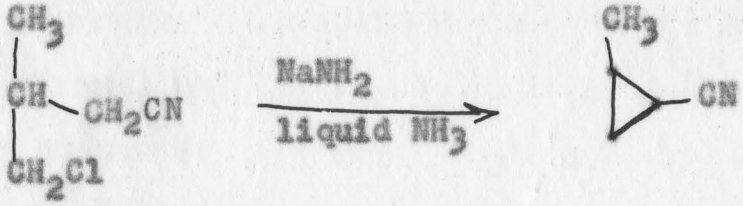
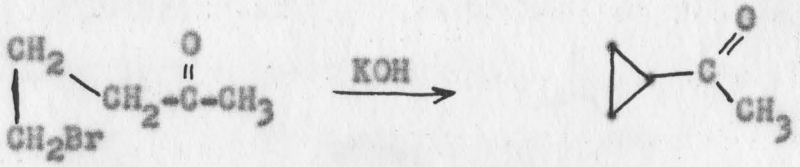
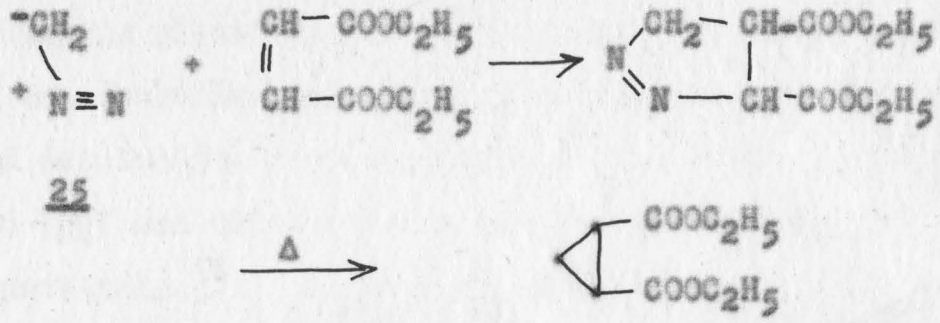
Gustavson[48] by substituting zinc and alcohol as the dehalogenating agent.

The cyclopropane ring may also be formed by intramolecular dehydrohalogenation; the reaction proceeds particularly well when the halide possesses an active methylene or methine group in the position beta to the halogen.[49,50]





Diazomethane (25) adds readily to α,β-unsaturated carbonyl compounds to form pyrazolines, which on pyrolysis lose nitrogen to afford cyclopropane derivatives.[51] Rinehart and Van Auken reported that



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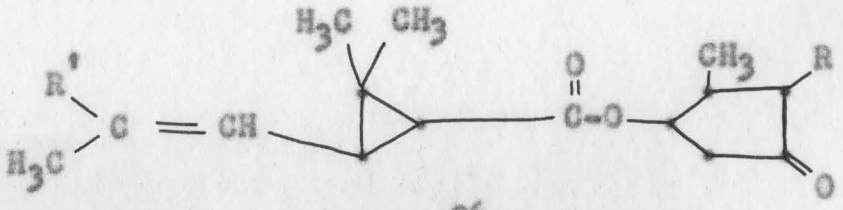
light-induced decomposition of the pyrazoline was free of side reactions and proceeded stereospecifically.[52,53]

The cyclopropane ring is rare in nature; indeed small rings in general are seldom found in natural products. The truxillic and truxinic acids isolated in 1889 by Liebermann were the first small ring compounds found in nature.[54] No further small ring compounds were reported until Staudinger and Ruzicka isolated from certain chrysanthemum flower heads two highly insecticidal components, pyrethrin I and pyrethrin II.[55] The two pyrethrins were characterized as esters represented by the general formula, 26. Each on



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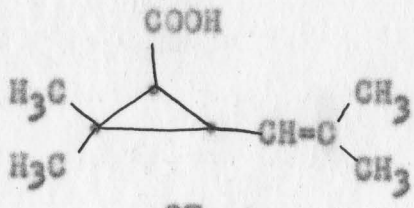
Pyrethrin I : R = CH_2-CH=CH-CH=CH_2 ; R' = CH_3

Pyrethrin II : R = CH_2-CH=CH-CH=CH_2 ; R' = $COOCH_3$

hydrolysis gives an acid derived from cyclopropane and a keto-alcoholic derivative of cyclopentane. The two acid derivatives from pyrethrin I and II are chrysanthemic acid (27) and chrysanthemum dicarboxylic acid (28), respectively.[56]



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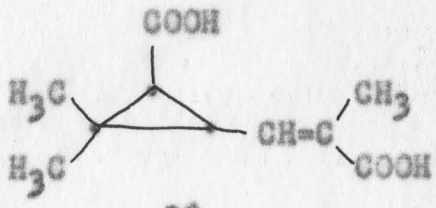
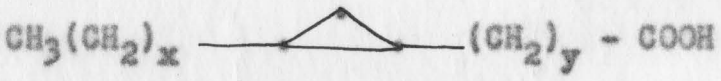


28

Before 1961 lactobacillic acid (29) was the only known naturally occurring fatty acid which contained the cyclopropane ring. It was isolated and recognized as such by Hofmann and Lucas.[57] Hofmann and co-workers[58] determined conclusively that the structure was as shown and that it had the cis configuration. Kosower[59] had earlier deduced the structure from biogenetic grounds with ricinoleic acid (32) as the suggested precursor. Liu and

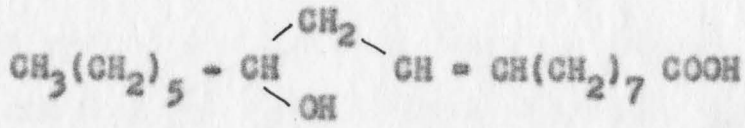


29 x = 5 ; y = 9

30 x = 5 ; y = 7

31 x = y = 7

Hofmann[60,61] however have recently proved that the biosynthesis of lactobacillic acid involves the



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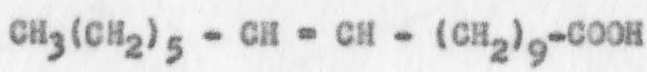


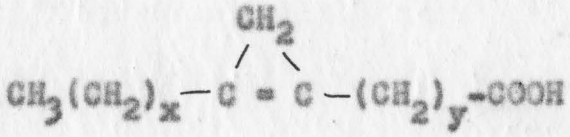
33

addition of a 1-C fragment across the double bond of cis-vaccenic acid (cis-11-octadecenoic acid) (33), a hemolytic fatty acid first found in the brain.[62]

In the past two years two additional cyclopropanoid fatty acids have been isolated. MacFarlane[63] and Kaneshiro and Marr[64] extracted from Escherichia coli a new fatty acid, 2-hexylcyclopropaneoctanoic acid (30), which represented twenty-two percent of the total fatty acids in E. coli. Wilson and co-workers[65,66] isolated from certain seed oils dihydrosterculic acid (2-octyl-cyclopropaneoctanoic acid) (31) by means of gas liquid chromatography.[67]

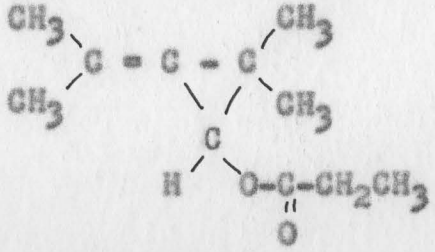
Closely related to these three cyclopropanoid fatty acids are several cyclopropenoid analogs. Sterculic

acid (34-a), the major acidic component of the seedfat of Sterculia foetida, isolated by Nunn[68] and assigned the indicated structure by Faure and Smith[69] and Rinehart,[70] was the first cyclopropenoid acid found in nature. Castellucci and Griffin[71] synthesized sterculic acid from its acetylenic precursor, stearolic acid. Hofmann[72] proved the cis configuration of dihydrosterculic acid by an unequivocal synthesis from cis-cyclopropane-1,2-diacetic acid. A homolog, malvalic acid (34-b), was later found in Malva seed oils.[73,74]



34-a : x = 7 ; y = 7
34-b : x = 7 ; y = 6

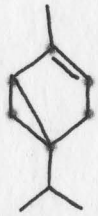
Jacobsen[75] recently announced the isolation of the sex attractant of the female cockroach. The structure of the attractant was shown to be 2,2-dimethyl-3-isopropylidinecyclopropylpropionate (35).



35

These five fatty acids, the insecticidal pyrethrins and the insect attractant are presently the only known naturally occurring compounds containing isolated cyclopropane rings. The cyclopropane system is much more frequently found fused with another ring in terpenoid compounds.

Derivatives of thujane and carane are prominent in various essential oils. Neither thujane nor carane has been found to occur in nature but their unsaturated analogs, α-thujene (36),[76] sabinene (37),[77] and 3-carene (38),[78] along with many keto and alcoholic derivatives are abundant in juniper oil and turpentine.



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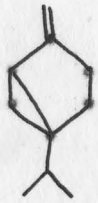

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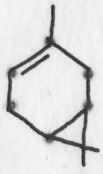
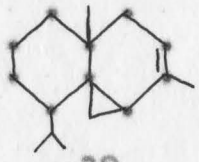


38

Sesquiterpenes and triterpenes containing the cyclopropane ring system have been isolated only in the past few years. More advanced identification techniques have resulted in some terpenes known for years by erroneous structures being correctly identified,[79] while

at the same time many new ones are being found due to better separation procedures.[66,80]

The four compounds whose structures are shown below represent the group of sesquiterpenes about which the most information is known. Thujopsene (39) and hinokiic acid (40), have been under extensive study since the turn of the century and were shown to be in various essential oils.[81,82] Their



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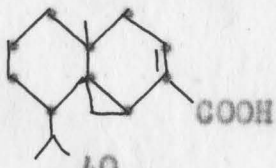

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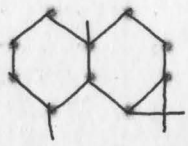

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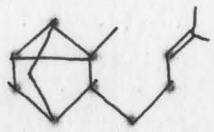
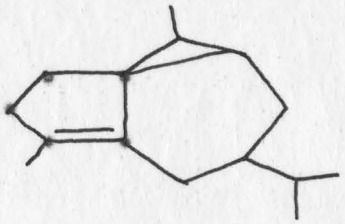


42

structure was determined only in 1960.[83,84] The structure of maaliol (41), found first in Maali resin obtained from a tree endemic to the Samoan Islands and recently in other essential oils,[80,85] has been completely elucidated.[86] The fourth, α-santalene (42)

found in sandalwood has been, along with many of its derivatives, thoroughly investigated.[87,88]

Other classes of cyclopropanoid sesquiterpenes include the derivatives of gurjunene (43)[79] isolated from the Gurjun balsam,[89] and aromadendrene (44).[90] Closely related to aromadendrene are the isomeric alcohols, ledol and globulol (45) whose complete



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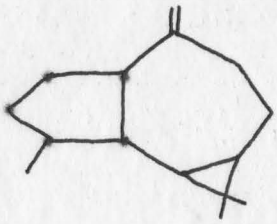

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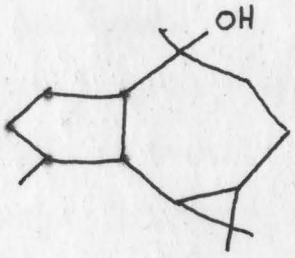

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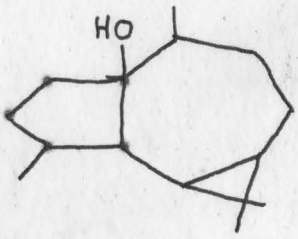
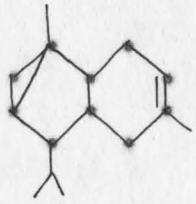


46

structure was determined by Dolejs in 1959.[91] Ledol was first isolated in 1875[92] and globulol in 1913.[93] The structure of palustrol (46), isolated only in 1954,[94] was determined in 1960.[95]

Copaene (47), a comparatively rare constituent of essential oils[96,97] was shown to have the structure shown by Briggs and Taylor.[98] Corbett and Speden[99] isolated cyclocolorenone (48) from a certain New Zealand shrub.



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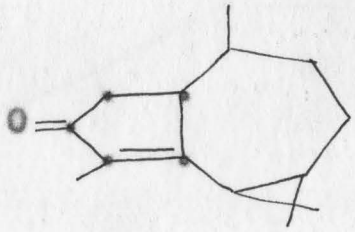
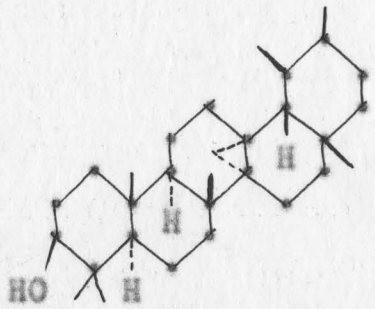


48

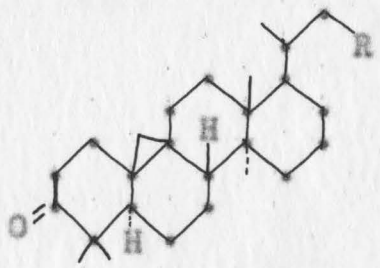
No cyclopropanoid diterpene has been isolated but several cyclopropanoid triterpenoid compounds have been isolated. The only hexacarbocyclic triterpene presently known, phyllanthol (49), was first isolated from the root-bark of Phyllanthus engleri, used as a poison by tribes of Rhodesia.[100] Phyllanthol was shown to be 13,27-cycloursan-3-β-ol by Barton[101] and Ruzicka.[102]



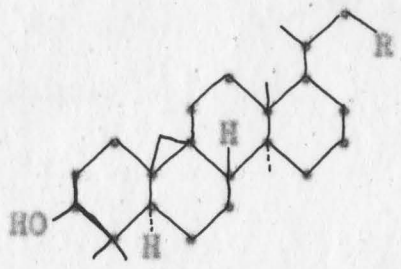
49

In addition to this one hexacarbocyclic triterpene, there are nine known naturally occurring cycloartane derivatives. Cycloartenone (50), isolated and characterized by Barton,[103] was the first cyclopropanoid triterpene found in nature. Since then cycloartenol (51) was found in Strychnos nux vomica,[104] cyclolaudenol (52) was isolated from opium,[105] cycloeucalenol (53) in Eucalyptus microcorys (Australian tallow wood),[106] and 24-methylenecycloartenol (54) in certain seed oils.[107] Djerassi and McCrindle[108] have isolated four new triterpenes (55-58) from Spanish moss.

Several years ago i-androstanolone (59) was isolated from the urine of patients with adrenocortical tumor;[109] this represents the only instance of a naturally occurring cyclopropanoid steroid.



50: R = $CH_2CH{=}C(CH_3)_2$



51: R = $CH_2CH{=}C(CH_3)_2$

52: R = $CH_2CH(CH_3)C(CH_3){=}CH_2$

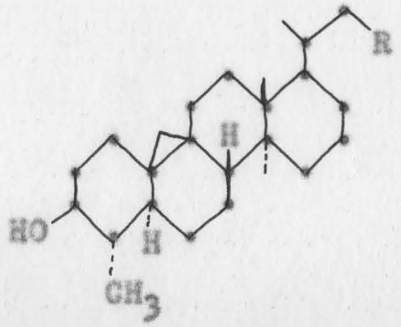
54: R = $CH_2C(=CH_2)CH(CH_3)_2$

55: R = $CH{=}CHC(CH_3)_2OH$

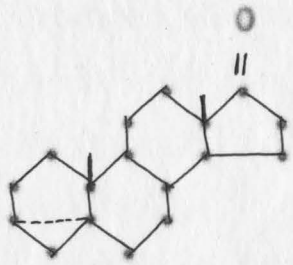
56: R = $CH_2CH(OH)C(=CH_2)CH_3$

57: R = $CH_2C(=O)C(=CH_2)CH_3$

58: R = $CH{=}CHC(CH_3)_2{-}OCH_3$



53: R = $CH_2C(=CH_2)CH(CH_3)_2$



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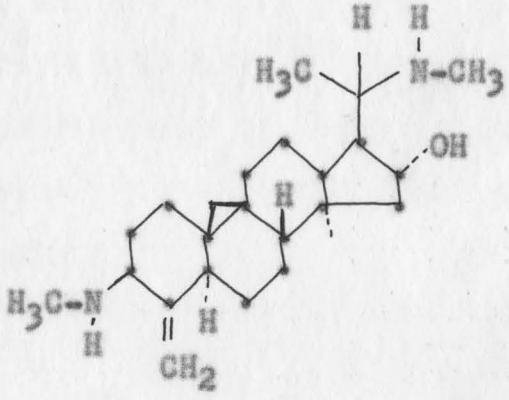
In the latter part of 1962, cyclobuxine (60) was isolated and characterized.[110] Cyclobuxine is the first steroidal alkaloid recognized to contain a cyclopropane ring.



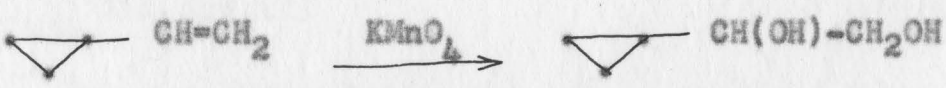
60

The interest in cyclopropane ring systems has been due in large part to the unique electronic properties caused by the arrangement of the three carbons in the ring. The double-bond character of the cyclopropane ring is well known; the ring may be

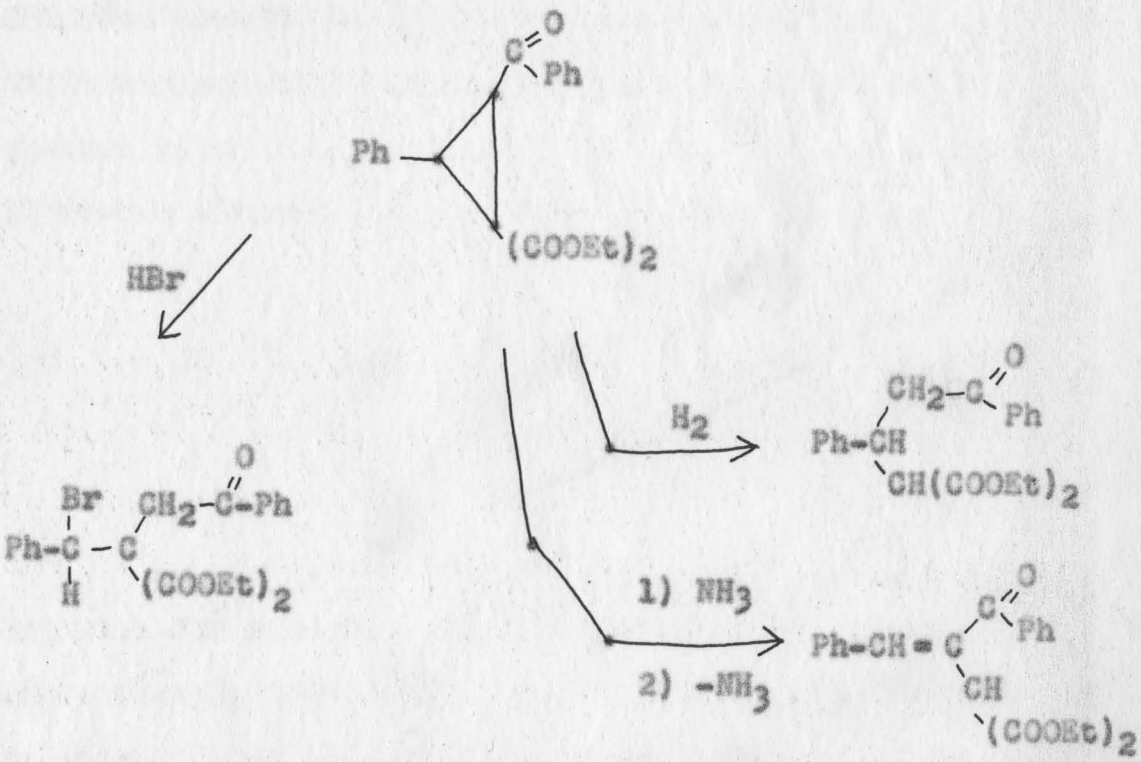
hydrogenated to yield propane derivatives,[111] it will react with bromine or iodine to form 1,3-dihalopropanes,[112,113] and halogen acids cause opening of the ring to give propyl halides.[114]

The ring opening follows the Markownikoff rule;[115] i.e., the ring opens between carbon atoms holding the smallest and largest number of alkyl groups, the major product being that in which the halogen is on the carbon with the most alkyl groups.

The color reaction with tetranitromethane characteristic of ethylenic compounds is also given by cyclopropane derivatives,[116] but cyclopropane derivatives are untouched by potassium permanganate. This difference was illustrated by Demjanov in the following reaction.[117]



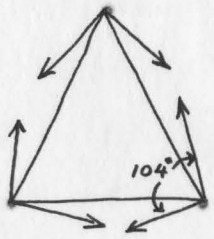
Concrete chemical proof of the existence of the three-membered ring in opposition to some normal ethylenic derivative was carried out by Kohler and Conant[114] by the fission of the ring at the three different sides.



A further analogy between the ethylene and cyclopropane systems is seen in the ability of the cyclopropane ring to conjugate with unsaturated groups.[114,118,119]

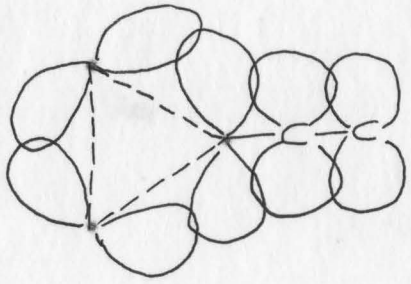
The pseudo-conjugate properties of the three-membered ring are borne out by dipole moment data.[120] They indicate that the C-C bond electrons in the ring are more weakly bound than the usual σ electrons and tend to exhibit characteristics associated with mobile π electrons. For maximum bonding interaction, the bonding orbitals of each carbon atom should be

directed toward the adjacent atoms necessitating a 60° angle between the orbitals of cyclopropane. However, quantum mechanics stipulates that the orbitals about a first-row element may not form an angle less than 90°,



and that for a carbon atom with four bonds an angle of approximately 109° is favored.[121] Coulson[122] has calculated that the best compromise involves an interorbital angle of 104° as shown above. This, in effect, means that the bonds between the carbons in cyclopropane are "bent" (banana bonds), and that the three regions of high electron density lie outside the triangle of carbon nuclei. These ring orbitals are thus rehybridized to $sp^{4.12}$ orbitals[37] instead of the usual tetrahedral sp^3 orbitals formed at 109° 18'. These bonds are shorter than normal, with the carbon-carbon bond distance being 1.526 Å compared to normal carbon-carbon bond distances of 1.54 Å.[123] The most important effect of these bent bonds is that the $sp^{4.12}$

orbitals are in a position to overlap with adjacent p orbitals of a double bond. This effect of conjugation (illustrated below for vinyl cyclopropane)[37] between adjacent p orbitals and three-membered rings is exhibited in the spectral patterns and reactions of cyclopropane systems. These effects will be discussed in detail in subsequent sections of this thesis.



DISCUSSION OF RESULTS

DISCUSSION OF RESULTS

A. Preparation of Starting Materials.

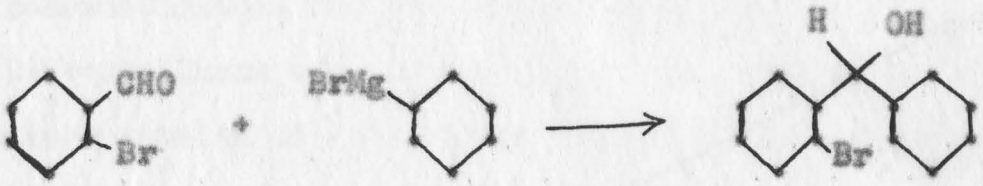
1. 2-Bromodiphenylmethane.

The usual method for preparing 2-bromodiphenylmethane (63) in This Laboratory is illustrated in Chart I. This method involves a reaction between 2-bromobenzaldehyde (61) and phenylmagnesium bromide followed by reduction of the resulting unisolated 2-bromodiphenylcarbinol (62).[124]

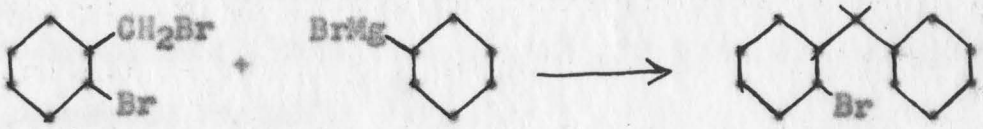
The 2-bromobenzaldehyde (61) was prepared by the side-chain bromination of 2-bromotoluene to 2-bromobenzal bromide followed by hydrolysis to the aldehyde.[125] An improvement by Polss in the preparation of this aldehyde has since been adopted in This Laboratory.[126]

Vingiello, Quo and Sheridan[127] demonstrated a new synthetic procedure which involves a cross-condensation reaction between aryl Grignard reagents and benzyl halides. Dissatisfaction with the lengthy work-ups and only moderate yields of the reaction between the Grignard reagent and aldehyde led to the application of the cross-condensation reaction to the preparation of 63.

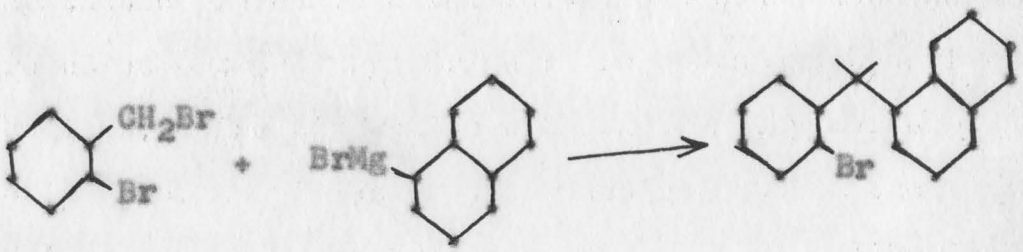
CHART I



61 62



64 63



64 65

The utilization of this reaction for the preparation of 2-bromodiphenylmethane (63) necessitated the preparation of 2-bromobenzyl bromide (64). At the outset of this investigation the required compound, 2-bromotoluene, was not commercially available. 2-Bromotoluene was, however, readily synthesized by diazotization of 2-toluidine followed by decomposition of the diazonium bromide with powdered copper.[128] The resulting 2-bromotoluene was converted to the desired 2-bromobenzyl bromide (64) by side-chain bromination with N-bromosuccinimide.[129]

The cross-condensation reaction between 2-bromobenzyl bromide (64) and phenylmagnesium bromide proceeded smoothly resulting in easier work-up and higher overall yield (42%) than was realized in the previously mentioned two-step reaction.

2. 2-(1-Naphthylmethyl)bromobenzene.

The reaction between 2-bromobenzaldehyde (61) and 1-naphthylmagnesium bromide followed by reduction of the resulting carbinol should give 2-(1-naphthylmethyl)bromobenzene. This method had been employed for several years in This Laboratory. Poor results in the reactions using this reaction product led Delia[130] to investigate the original reaction between the Grignard

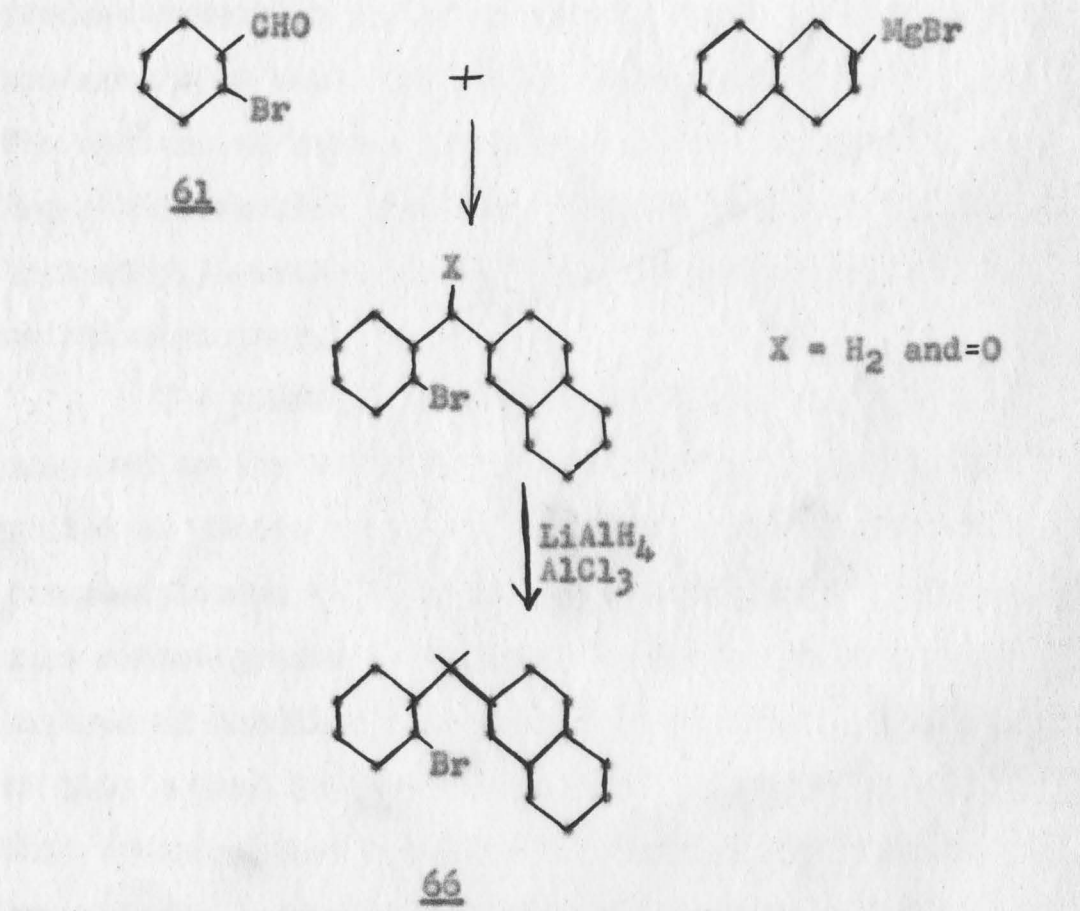
reagent and the aldehyde. Delia found that instead of the expected carbinol, this reaction yielded a mixture of the corresponding methylene compound and ketone. Since Delia was investigating the anomalous products from this reaction sequence, the problem was circumvented by preparing the desired 2-(1-naphthylmethyl)bromobenzene (65) as indicated in Chart I by the cross-condensation reaction which had proved very efficient in the case of 2-bromodiphenylmethane (63). The greater overall yield of the product and the shorter time involved in its preparation by the cross-condensation reaction make this method superior to the reaction sequence involving the aldehyde. Both this preparation and that for 2-bromodiphenylmethane are now in general use in This Laboratory.

3. 2-(2-Naphthylmethyl)bromobenzene.

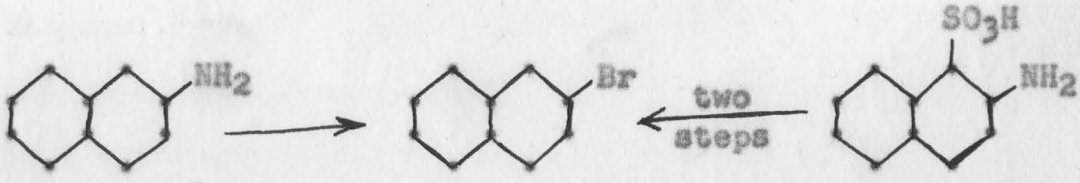
A cross-condensation reaction analogous to that used in the preparation of 2-(1-naphthylmethyl)bromobenzene (65) is not applicable for the preparation of 2-(2-naphthylmethyl)bromobenzene (66). When 2-naphthylmagnesium bromide was treated with 2-bromobenzyl bromide the self-coupling of the Grignard reagent was the major reaction.

The reaction between 2-bromobenzaldehyde and 1- or 2-naphthylmagnesium bromide, expected to give the corresponding secondary alcohol, has been shown by Delia[130] and Polss[131] to produce none of the alcohol but instead to give a mixture of the corresponding ketone and methylene compound shown in Chart II. The generally overlooked observation of Marshall[132] could be the cause of the anomalous products. Marshall observed that only when an aldehyde in less than equivalent proportions was allowed to react with an alkylmagnesium halide was the expected secondary carbinol the chief product of the reaction. Marshall further observed that benzyl alcohol and benzophenone were the only products from the reaction of excess benzaldehyde with phenylmagnesium bromide. However, Marshall did not report the isolation of any methylene compound. Furthermore, Polss[131] could find no evidence of any alcohol in the case of the naphthylmagnesium bromides. The most likely explanation of these anomalous product-formations according to Polss is that the desired intermediate carbinol forms and then in some manner is altered by unreacted starting material; Marshall suggested that the excess aldehyde combined with the magnesium complex. Since the ratio of methylene compound to ketone is not a 1:1 ratio,[131] simple

CHART II



61 66



67 69 68

disproportionation does not appear to be the answer. Work is to be continued in This Laboratory to answer this question. Even though the reason for the anomalous product-formation is not presently known, the unexpected products have been completely characterized by Polss. The mixture of ketone and methylene compound obtained from this reaction was reduced to the desired 2-(2-naphthylmethyl)bromobenzene (66) by the method of Blackwell and Hickinbottom.[133]

The prerequisite 2-bromonaphthalene (69) was prepared by the two methods illustrated in Chart II. The method of Newman and Wise[134] involves the diazotization of 2-naphthylamine (67), a potent carcinogen.[135] Although this method generally resulted in higher yields, the hazards of handling 2-naphthylamine led to the abandonment of this method in favor of that of Wolfe and Doukas.[136] This second method resulted in lower yields but was amenable to larger scale preparations thus eliminating much of the repetitiveness of the Newman and Wise method. However, Polss[137] later showed that the low yield of Grignard reagent formation from the product obtained from the Wolfe and Doukas method was due to the formation of 2-chloronaphthalene as the major product rather than

the expected 2-bromonaphthalene. Polss[137] modified the Wolfe and Doukas method to eliminate the chloro compound.

4. 2-Benzyl-1-bromonaphthalene.

Due to the previously discussed difficulties encountered in the preparation of 2-(2-naphthylmethyl)-bromobenzene (66) in addition to the fact that subsequent Grignard reagent formation from this compound was of low yield, the isomeric disubstituted naphthalene (76) was prepared. The Grignard reagent obtained from 2-benzyl-1-bromonaphthalene (76) would result in a ketone, 70, (see Chart III), which would result in the identical cyclized product, 72, obtained from its isomeric ketone, 71. The cyclization of ketone 70 would be more difficult to effect than that of ketone 71 due to the well-known[138] ease of cyclization into the α-position of a naphthyl group in comparison to cyclization into a phenyl group. In spite of this drawback 2-benzyl-1-bromonaphthalene appeared to be the superior reagent due to preparative facility. The cross-condensation reaction between the appropriate benzyl halide and a Grignard reagent as illustrated in Chart IV proceeded smoothly and in good yield.

The bromination of commercially available 2-methylnaphthalene (73) gave in good yield

CHART III

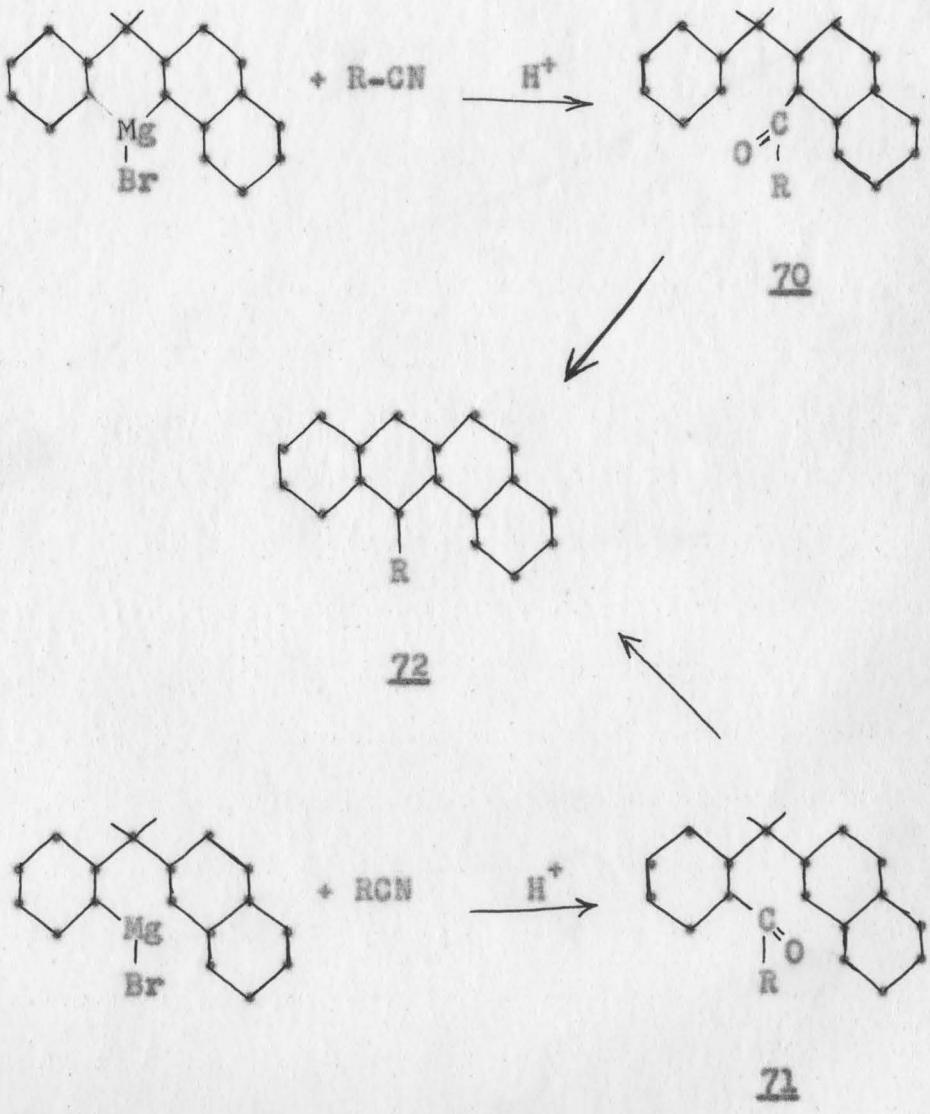
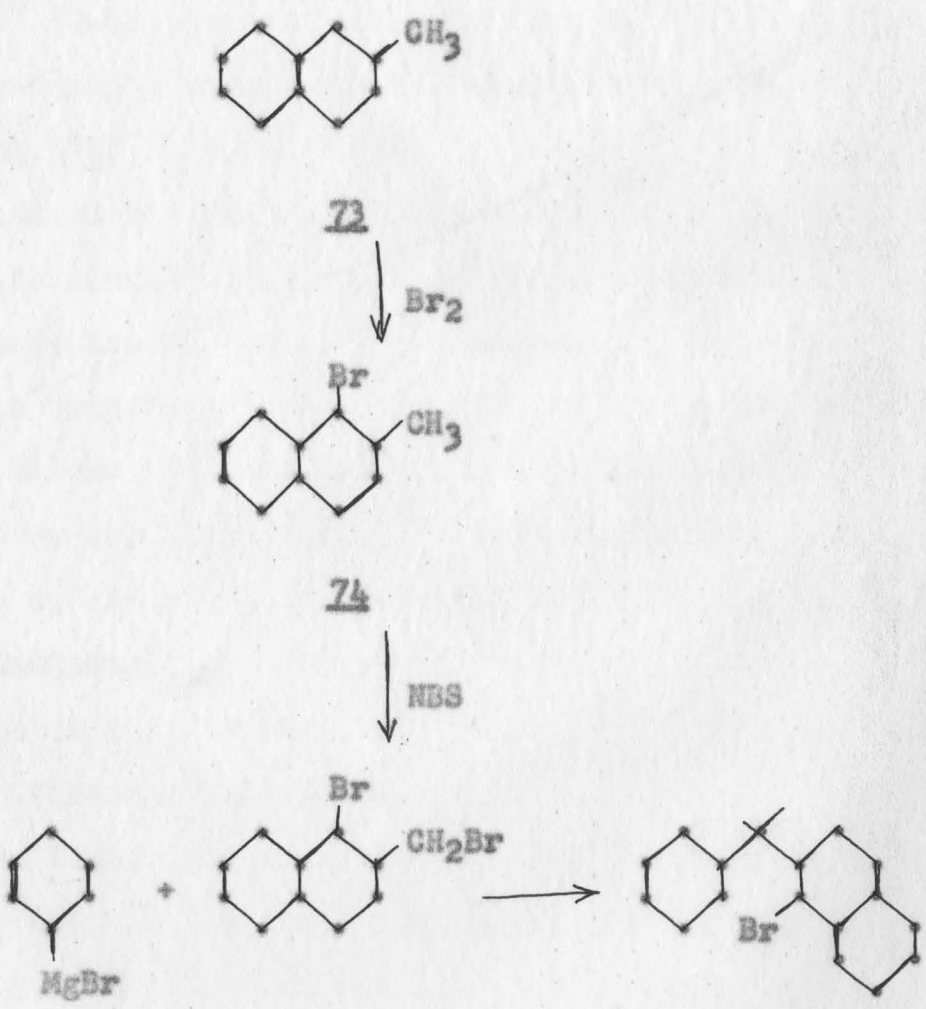


CHART IV



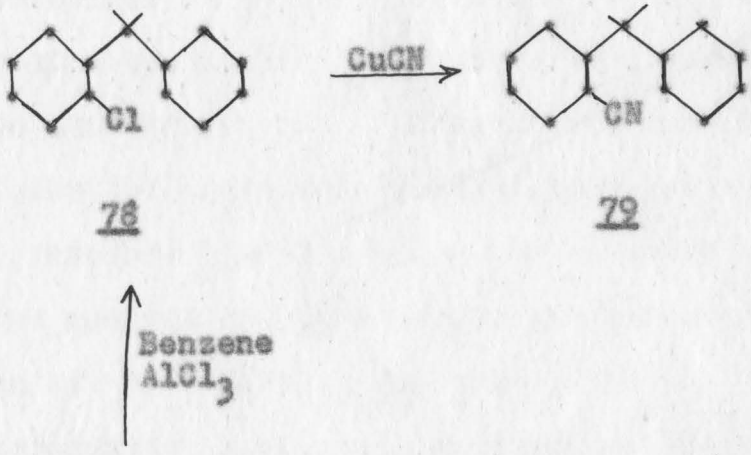
1-bromo-2-methylnaphthalene (74). Side-chain bromination of 1-bromo-2-methylnaphthalene using the Schmid-Karrer modification[139] of the Wohl-Ziegler reaction[140] (N-bromosuccinimide with benzoyl peroxide as the brominating agent) gave 1-bromo-2-bromomethylnaphthalene (75) in good yield.

Since 2-benzyl-1-bromonaphthalene could not be conveniently distilled at the same pressure as reported in the literature (10^{-4}mm.),[204] a derivative of this product was prepared. The cyano derivative, 2-benzyl-1-cyanonaphthalene (77) was prepared using the standard Rosenmund-von Braun reaction.[141] This product was identified by elemental analysis and its infrared spectrum indicated the presence of the nitrile group (absorption at 4.5 microns).

5. 2-Cyanodiphenylmethane.

The Rosenmund-von Braun reaction[141] is used in This Laboratory as a general method of preparing cyano derivatives of aryl compounds. The prerequisite chloro compounds are readily prepared with generally high yields. The reaction scheme illustrated in Chart V was employed for the preparation of 2-cyanodiphenylmethane (79). The corresponding 2-chlorodiphenylmethane (78) was prepared

CHART V



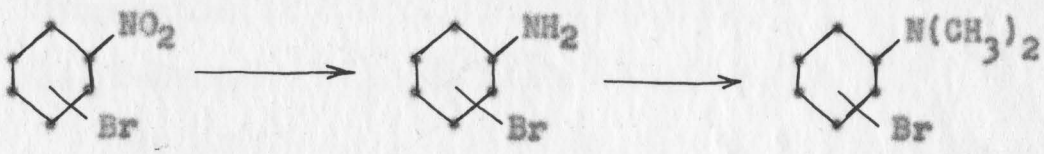
by means of a Friedel-Crafts reaction[142,143] between 2-chlorobenzyl chloride and benzene.

6. 2-(1-Naphthylmethyl)benzonitrile.

The general method of preparing 2-(1-naphthylmethyl)benzonitrile (81) involves the replacement of a chlorine atom by a cyano group using the procedure of Rosenmund and von Braun.[141] The preparation of the prerequisite 2-(1-naphthylmethyl)chlorobenzene (80) formerly involved the time consuming reaction between a Grignard reagent and an aldehyde and subsequent reduction of the resulting carbinol. The cross-condensation reaction described by Vingiello, Quo and Sheridan[127] was applied to the preparation of this chloro compound. The reaction sequence as illustrated in Chart V proceeded quite smoothly and is now in general use in This Laboratory.

7. 2- and 3-Bromodimethylanilines.

While 4-bromodimethylaniline was readily available commercially, neither the 2- nor the 3-isomer was. These two compounds were synthesized using the procedure as shown below. The corresponding nitro compounds were reduced to the amino compounds and then methylated with methyl sulfate.



82 : 2-isomer	84 : 2-isomer	86 : 2-isomer
83 : 3-isomer	85 : 3-isomer	87 : 3-isomer

The method of Hazlet and Dornfeld[144] gave nearly quantitative yields of 2-bromoaniline (84) from the corresponding nitro derivative (82) by reduction with activated iron. The method of Natelson and Gottfried,[145] using mossy zinc and hydrochloric acid, was adopted for the reduction of both isomeric bromonitrobenzenes to 2-bromoaniline (84) and 3-bromoaniline (85). This method, even though it resulted in a considerable decrease in yield, was preferred to that of Hazlet and Dornfeld because it was adaptable to large scale preparations. Apparently, the preparation of the activated iron was not feasible for larger amounts than ten grams (see Experimental Section).

Both 2- and 3-bromodimethylaniline (86,87) were prepared from the corresponding free amines using the standard Gilman and Banner[146] method utilizing dimethyl sulfate as the methylating agent.

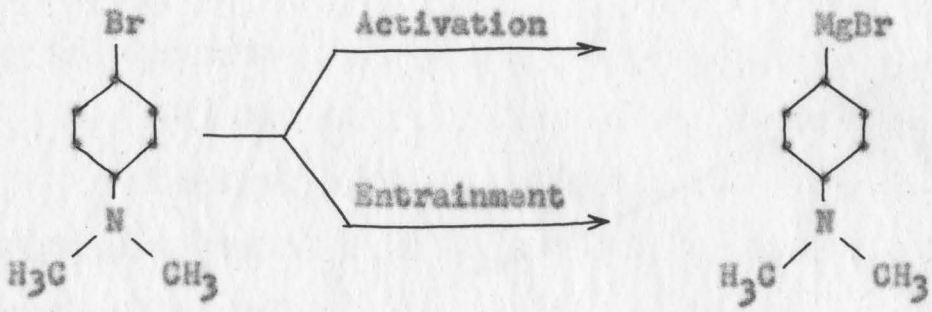
B. Preparation of Ketones and Pyrrolines.

1. 2-Benzyl-4'-dimethylaminobenzophenone.

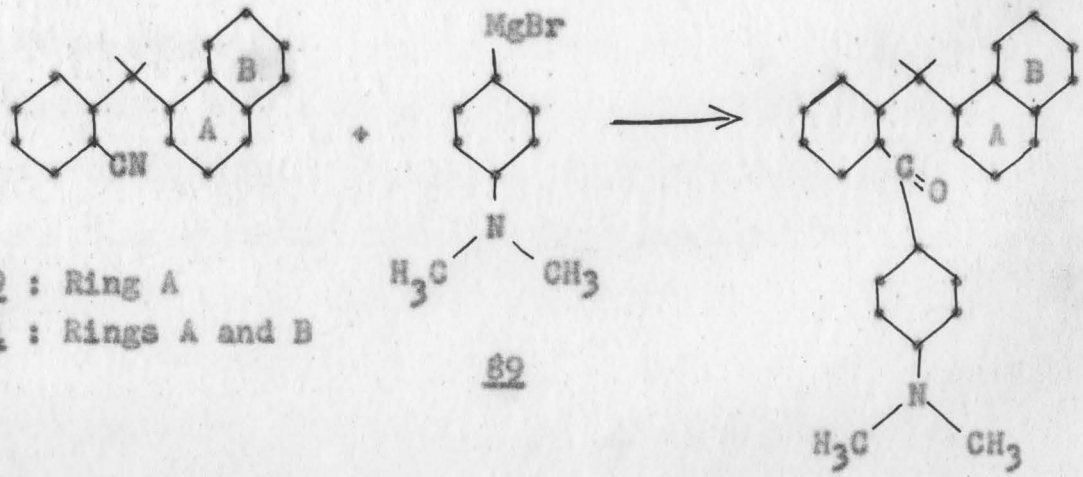
The preparation of 2-benzyl-4'-dimethylaminobenzophenone (90) fulfilled a two-fold objective. Besides giving a new ketone intermediate for the synthesis of a new anthracene derivative, this preparative scheme (illustrated in Chart VI) gave an indication of its applicability in more complex systems while utilizing a relatively expendable starting material - 2-cyanodiphenylmethane (79).

4-Bromodimethylaniline (88) will not form a Grignard reagent under normal conditions even after activation of the magnesium with iodine and several days of warming the reaction mixture.[147] Several modifications of the usual method[148] of Grignard reagent formation have been reported. One of these, developed by Ehrlich and Sachs,[149] involved activation by ethyl bromide and ethylmagnesium bromide. A second method of preparing 4-dimethylaminophenylmagnesium bromide (89) is a modification[150] of Grignard's "entrainment" technique[151] (see Section B.2, Discussion of Results). Both of these methods were employed during this investigation to prepare the Grignard reagent 89. Essentially identical results were obtained from each method.

CHART VI



88 89



79 : Ring A
81 : Rings A and B

89

90 : Ring A
91 : Rings A and B

Upon addition of 2-cyanodiphenylmethane (79) to 4-dimethylaminophenylmagnesium bromide (89) followed by hydrolysis of the magnesium complex, the desired ketone 90 was obtained. The ketone was characterized by its infrared spectrum and elemental analysis.

2. 2-(1-Naphthylmethyl)-4'-dimethylaminobenzophenone.

The Davies and Mann modification[150] of the entrainment method mentioned in the previous section was eventually adopted as the method of preparing 4-dimethylaminophenylmagnesium bromide (89). This method gave no better yield of the Grignard reagent than did the activation method but it was mechanically easier to achieve. The proportions of reagents used (nitrile - 1 mole, bromoaniline - 3 moles, ethyl bromide - 1.3 moles, magnesium - 6.7 g. atoms) ensured an excess of magnesium over the two bromo compounds and an excess of the total Grignard reagents over the nitrile. Davies and Mann showed that the desired Grignard reagent was formed in sixty percent yield with such a mixture.

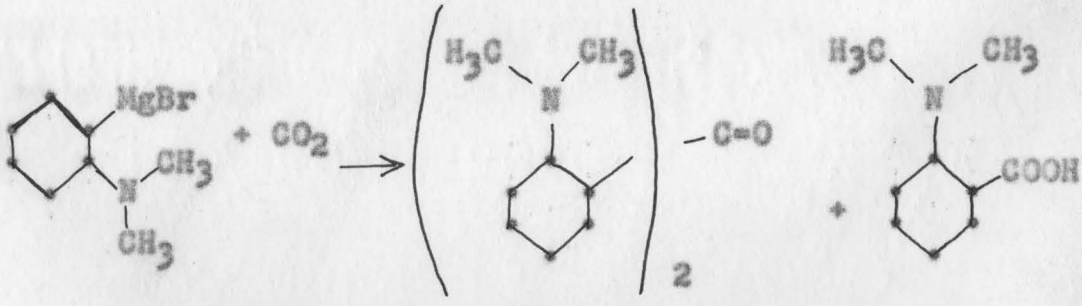
Treatment of this Grignard reagent mixture gave in forty-five percent yield the desired new ketone, 2-(1-naphthylmethyl)-4'-dimethylaminobenzophenone (91), which was characterized by its infrared spectrum and elemental analysis.

Spectral data on ketone 91 and the other dimethylamino substituted benzophenones synthesized will be discussed in a subsequent section of this thesis.

3. 2-(1-Naphthylmethyl)-2'-dimethylaminobenzophenone.

The preparation of 2-(1-naphthylmethyl)-2'-dimethylaminobenzophenone (92) was effected in greatly reduced yield in the same manner as its 4-dimethylamino isomer 91 (see Chart VI). Although the Grignard reagent of 2-bromodimethylaniline (86) may be prepared in reasonable yield by entrainment with ethyl bromide,[152] the Grignard reagent has been reported to give anomalous products.

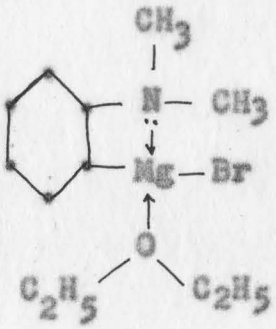
Holmberg[153] reported the isolation of 2,2'-di-(dimethylamino)benzophenone (93) in fifty-eight percent yield along with eighteen percent yield of the expected acid (94) from the carbonation of the Grignard reagent



93 94

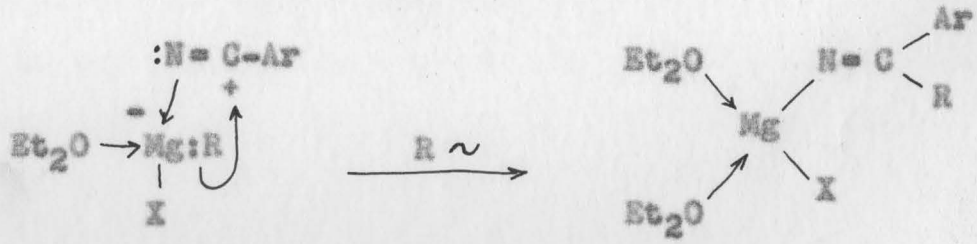
of 2-bromodimethylaniline (86). Holmberg attributed the formation of ketone 93 to the formation of strained planar rings through complex magnesium-nitrogen bonds in the Grignard reagent.

Such participation of the amino nitrogen in the Grignard reagent (95)[150] in place of one of the ether oxygens normally so involved might possibly explain the low yield of 2-(1-naphthylmethyl)-2'-dimethylaminobenzo-



95

phenone (92). Swain[154] has proposed the following mechanism for the reaction between Grignard reagents and aromatic nitriles, with intramolecular rearrangement



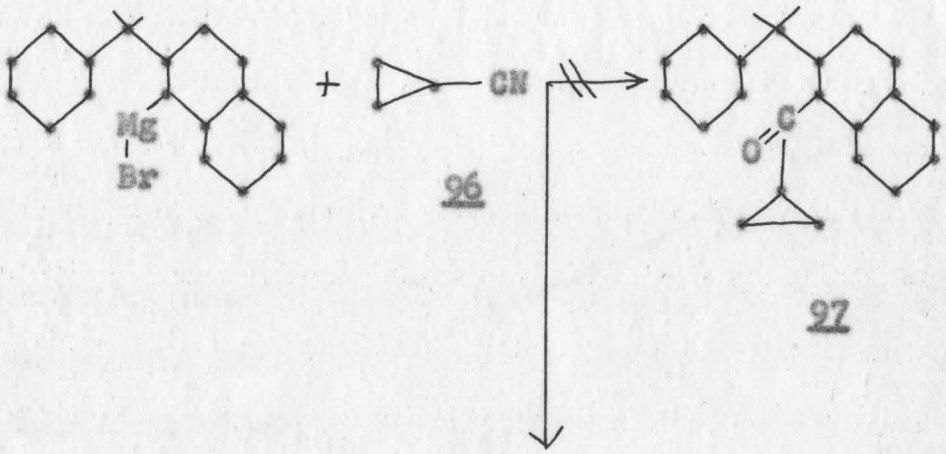
the rate-determining step. It appears quite feasible that, if the Grignard reagent does exist as pictured above (95), the migration of the dimethylaminophenyl group doubly attached to the magnesium atom would be seriously hindered.

4. 2-Benzyl-1-(2-Δ^1-pyrrolinyl)naphthalene.

Attempts to prepare cyclopropyl 1-(2-benzyl)-naphthyl ketone (97) by the standard procedure of nitrile addition to a Grignard reagent gave unexpected results. As illustrated in Chart VII the reaction between cyclopropyl cyanide (96) and 2-benzyl-1-naphthyl-magnesium bromide produced no identifiable ketone but a sixty percent yield of 2-benzyl-1-(2-Δ^1-pyrrolinyl)-naphthalene (98).

Although unexpected, the isolation of a pyrroline derivative was, on hind-sight, not surprising. Cloke[155] reported in 1929 the thermal rearrangement of cyclopropyl phenyl ketimine (100) or its hydrochloride salt to 2-phenylpyrroline (101). Cloke made no designation of the position of unsaturation in the pyrroline ring other than to say that the product was an equilibrium mixture between the Δ^1-isomer (101) and the Δ^2-isomer. There

CHART VII



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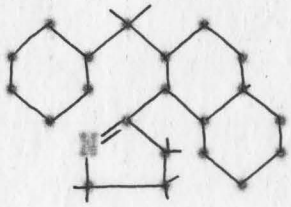
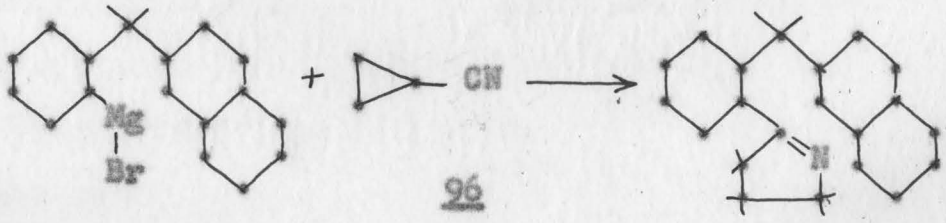
97

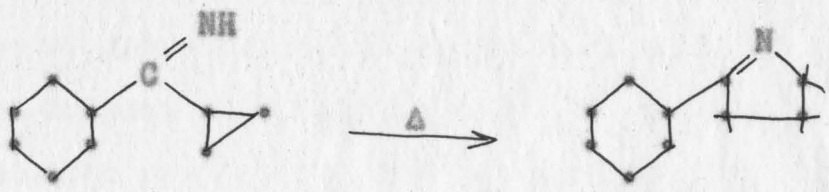


98



96

99



100 101

has been considerable confusion[156] in the literature concerning this supposed equilibrium between the two isomers, and only recently has concerete evidence for the distinction between the two forms been reported. Recent investigations have cast doubt on whether the Δ^2-pyrroline system ever exists. Zerewitinoff determinations[157] on questionable pyrrolines showing in all cases no available active hydrogen established the existence of the Δ^1-form, which unlike the Δ^2-form, has no active hydrogen attached to the ring nitrogen. Bonnett[158] showed by means of infrared analysis of questionable pyrrolines no absorption in the N-H region, but a strong band attributed to C=N absorption in the 1620-1650 cm.$^{-1}$ region was present. Proton magnetic resonance spectra[159] support the Δ^1-form by demonstrating the lack of signal in the olefinic proton region for eight 2-alkyl-Δ^1-pyrrolines.

Elemental analysis alone does not prove the existence of 2-benzyl-1-(2-Δ^1-pyrrolinyl)naphthalene (98) since the compound is isomeric with its precursor ketimine. The possibility of the presence of unrearranged ketimine in the product was eliminated by infrared analysis which showed no absorption in the N-H region. When the product was subjected to normal hydrolysis conditions, no corresponding ketone could be isolated.

The tendency of Δ^1-pyrrolines to polymerize has been reported.[156] Several observations by this author indicate that this pyrroline derivative (98) also polymerized upon standing in air. An alcoholic solution of the product turned red immediately and a similar red color appeared after several hours when the product was dissolved in carbon tetrachloride. The product which distilled as a slightly yellow oil solidified on standing, but when the solid was left unsealed, within a week it too would become colored. The dark red color could be removed only by distillation resulting in considerable loss of product.

Final conclusive evidence that the pyrroline structure was present was obtained by the selenium dehydrogenation[160] of the pyrroline to a pyrrole derivative. The resulting pyrrole was identified by means of a

specific spot test described by Feigl.[161] The positive test as manifested by the production of a yellow-brown dye was observed when the pyrrole was treated with fluorescein chloride.

5. 2-(2-Δ^1-Pyrrolinyl)phenyl-2-naphthylmethane.

Since cyclopropyl 1-(2-benzyl)naphthyl ketone (97) could not be prepared by the method described in the preceding section, its isomer, cyclopropyl 2-(2-naphthylmethyl)phenyl ketone (102), (see Chart III) had to be prepared in order to obtain a ketone precursor for attempted cyclization to give 12-cyclopropylbenz[a]anthracene.

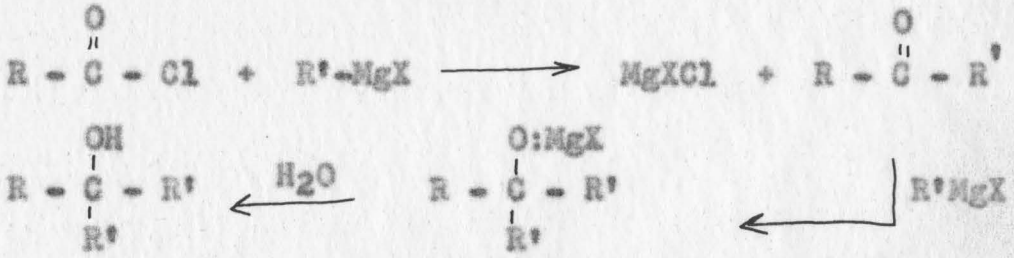
The reaction between the Grignard reagent of 2-(2-naphthylmethyl)bromobenzene and cyclopropyl cyanide (see Chart VII) did not give the desired ketone (102), but again the rearrangement of the intermediate ketimine occurred before hydrolysis resulting in the formation of 2-(2-Δ^1-pyrrolinyl)phenyl-2-naphthylmethane (99) in forty-five percent yield. The infrared spectrum of this pyrroline derivative was quite similar to that of 2-benzyl-1-(2-Δ^1-pyrrolinyl)naphthalene (98) (see Appendix) and had no absorption in the N-H region. This product was stable in hydrolysis media and exhibited

similar polymerization in air in the same manner as did its isomer which was discussed in the preceding section.

Along with the pyrroline derivative, a minute amount of 5-cyclopropylnaphthacene (103) was isolated. This product separated in about one percent yield from an alcoholic solution of the pyrroline derivative. This product was identified by its elemental analysis and ultraviolet spectrum. This occurrence will be discussed fully in Section C.5, Discussion of Results.

6. Substituted cyclopropyl phenyl ketones.

Since the reaction between Grignard reagents and nitriles failed to produce the desired ketones, another method of preparation was needed. Recent success in preparing ketones by inverse addition of Grignard reagents to acid chlorides has been reported by Ojakaar[162] and Polss.[163] The reaction between a Grignard reagent and an acid chloride was first reported by Tissier and Grignard[164] for the production of tertiary alcohols. The ketone intermediate may be isolated from the reaction medium by using inverse addition of the Grignard reagent to the acid chloride. The effect of a small amount of Grignard reagent in contact with a large excess of acid chloride minimizes the reaction of a second molecule of Grignard reagent



with the ketone. Steric hindrance will also prevent the second molecule of Grignard reagent from attacking the ketone.[165]

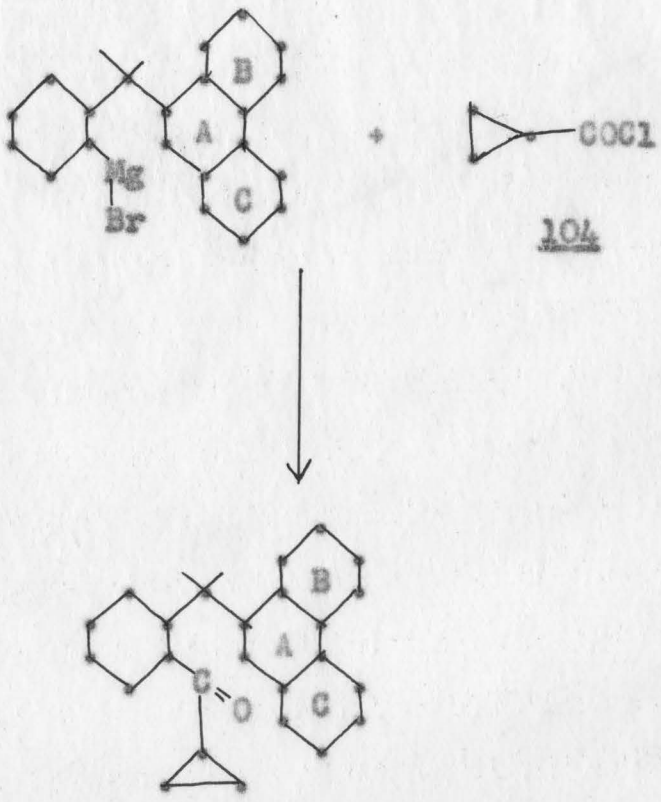
The appropriate Grignard reagents were added to cyclopropanecarboxylic acid chloride (104) as illustrated in Chart VIII. The corresponding three new ketones, cyclopropyl 2-(2-naphthylmethyl)phenyl ketone (102), cyclopropyl 2-(1-naphthylmethyl)phenyl ketone (105) and cyclopropyl 2-benzylphenyl ketone (106), were isolated in good yield. These three ketones were characterized by elemental analysis and infrared spectra (see Section D.1, Discussion of Results).

C. Preparation of Cyclized Materials.

1. 4-Dimethylaminophenyl substituted anthracene and benz[a]anthracene.

The Bradsher method[166] of aromatic cyclodehydration was employed for the synthesis of these two

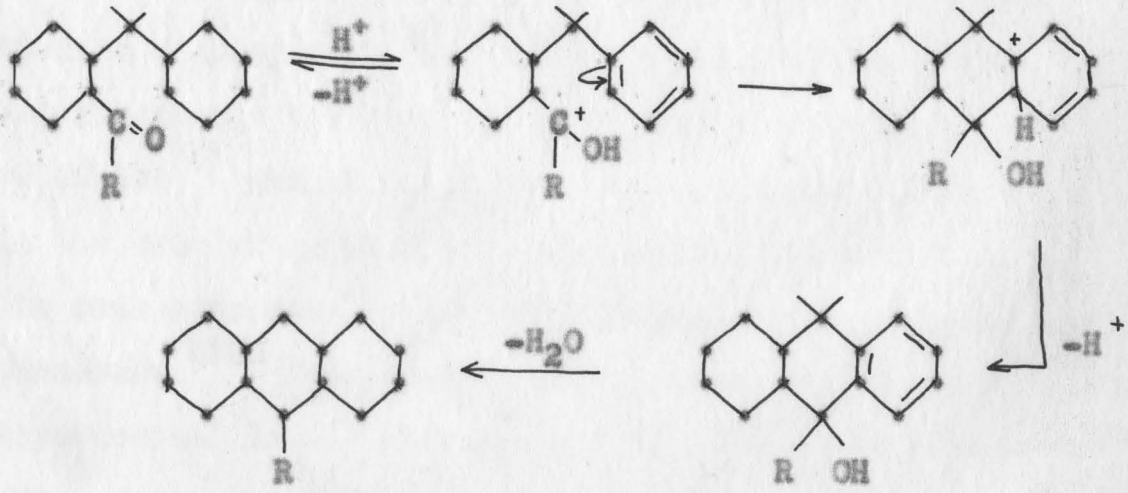
CHART VIII



102 : Rings A and C
105 : Rings A and B
106 : Ring A

compounds. A mechanism of this cyclization was postulated by Bradsher and Vingiello in 1949.[167] They postulated a mechanism which proceeds through four steps.

a) the reversible addition of a proton to the carbonyl oxygen,
b) reaction between the resulting carbonium ion and the ortho-position of the ring into which cyclization is to occur,
c) elimination of a proton, and finally
d) transannular elimination of water.



The acid catalyst most widely used for these cyclodehydration reactions is a mixture of hydrobromic acid, acetic acid and water. The mixture is usually prepared by mixing appropriate amounts of forty-eight percent hydrobromic acid with glacial acetic acid.

Both 7-(4-dimethylaminophenyl)benz[a]anthracene (107) and 9-(4-dimethylaminophenyl)anthracene (108) were

prepared quantitatively from their corresponding ketones using the standard acid catalyst (see Chart IX).

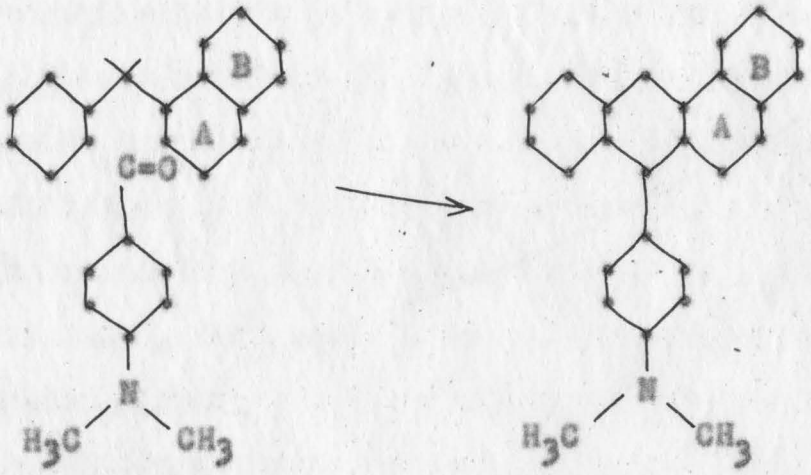
Bradsher and Vingiello[167] stated that there are involved in this type of aromatic cyclodehydration two steps of opposing electrical requirements. Vingiello, Van Oot and Hannabass[168] reported a general indication that the second step is the more susceptible to substituent effects than is the first step.

The dimethylamino group exists as a positively charged dimethylammonium ion under the conditions of the reaction. This exerts an extremely powerful -I effect[169] which should cause a considerable increase in the rate of cyclization. Evidence of such effects in the rate have been reported by Vingiello, Van Oot and Hannabass.[168] This prediction was borne out by experimental data. Although no rate measurements were made, these two ketones cyclize quantitatively in less than one hour under conditions for which average reaction time is eight hours for other substituents.[168]

2. 7-(3-Dimethylaminophenyl)benz[a]anthracene.

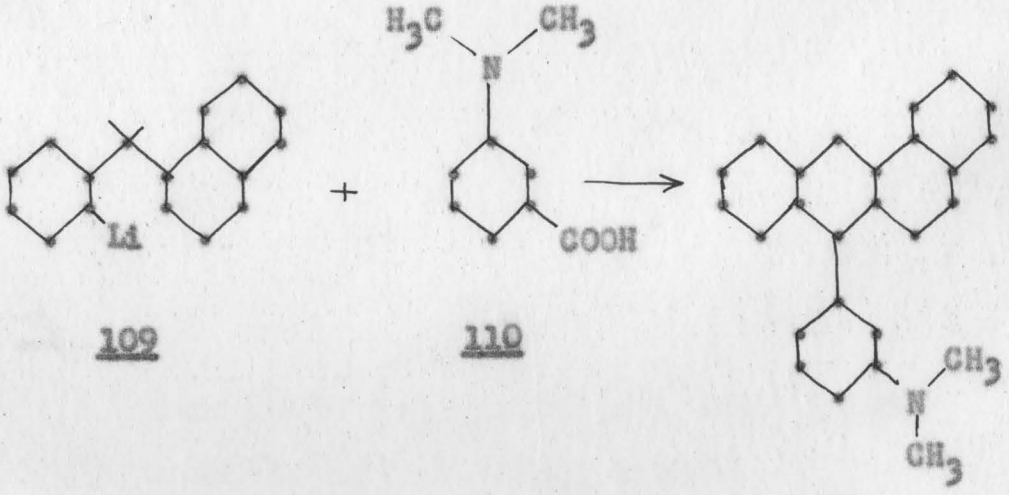
Attempts to prepare 7-(3-dimethylaminophenyl)-benz[a]anthracene (111) by the same procedure used for the 4-dimethylamino isomer were unsuccessful. All attempts to prepare the Grignard reagent of

CHART IX



91 : Rings A and B
90 : Ring A

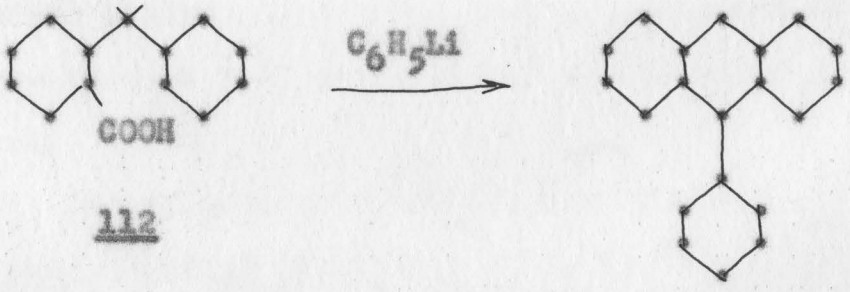
107 : Rings A and B
109 : Ring A



109 110 111

3-bromodimethylaniline failed. There is no indication in chemical literature that it has ever been prepared. Repeated attempts were then made to prepare 3-dimethylaminobenzoyl chloride but when 3-dimethylaminobenzoic acid (110) was treated with thionyl chloride only an intractable tar was obtained which decomposed further on distillation. Since the ketone could not be made by ordinary means (Grignard reagent with either nitrile or acid chloride), Bradsher's base-catalyzed cyclization[170] was applied directly to the synthesis of 7-(3-dimethylaminophenyl)benz[a]anthracene (111).

Bradsher[170] reported the preparation of 9-phenylanthracene (113) from the treatment of 2-benzylbenzoic acid (112) with phenyllithium.



112 113

Since 3-dimethylaminobenzoic acid (110) was already available in This Laboratory, it was treated

with 2-(1-naphthylmethyl)phenyllithium (109) as illustrated in Chart IX. 7-(3-Dimethylaminophenyl)-benz[a]anthracene (111) was obtained in a very poor yield of fifteen percent.

3. Attempted Preparation of 7-(2-Dimethylamino-phenyl)benz[a]anthracene.

The treatment of 2-(1-naphthylmethyl)-2'-dimethylaminobenzophenone (92) with the standard hydrobromic acid-acetic acid-water mixture did not give the desired product. That cyclization did occur was evidenced by the fact that an ultraviolet spectrum of the reaction mixture indicated a benz[a]anthracene system. The product was a tarry mass which, following continued purification steps, yielded a minute amount of benz[a]anthracene and a low-melting material whose elemental analysis indicated that considerable cleavage had occurred (a very small percentage of nitrogen was present).

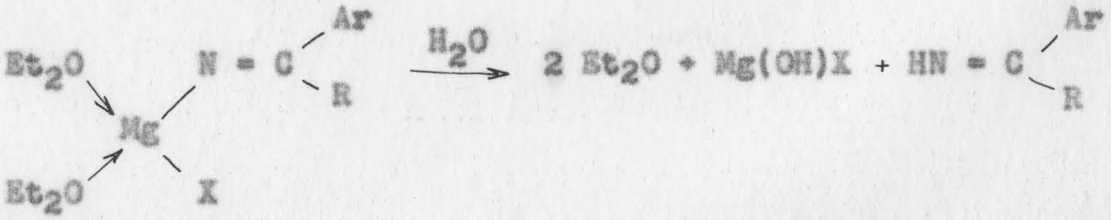
Such cleavage is not unknown in cyclization of ortho-substituted meso phenylbenz[a]anthracenes; there have been several instances reported in This Laboratory.[30,171,172] The explanation seems to be steric interference of the ortho-substituent with the flanking 6- and 8-hydrogens of the aromatic nucleus.

Vingiello and Delia[172] also reported the possibility of cleavage after cyclization.

4. 7-Cyclopropylbenz[a]anthracene.

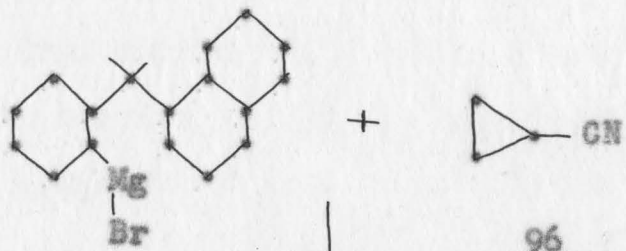
Several methods were used with varying degrees of success to prepare 7-cyclopropylbenz[a]anthracene (114). The most successful of the two general methods illustrated in Chart X was an unexpected reaction.

The isomeric Grignard reagents (see Chart VII and Sections B.4 and B.5, Discussion of Results) upon treatment with cyclopropyl cyanide gave pyrrolines 98 and 99. However, when 2-(1-naphthylmethyl)phenylmagnesium bromide was treated with cyclopropyl cyanide, the only identifiable product was the cyclized material 114. The hydrolysis of the Grignard complex was originally effected by excess aqueous ammonium chloride. Such hydrolysis must pass through a ketimine intermediate.

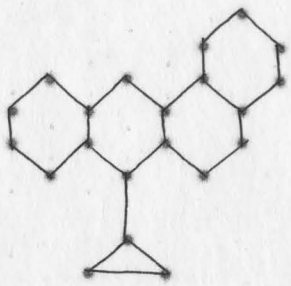


Whether such a ketimine intermediate undergoes further hydrolysis to the corresponding ketone depends on the

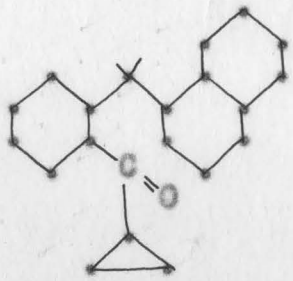
CHART X



96



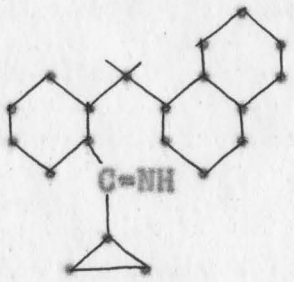
114



105

nature of both the compound and the hydrolysis medium.[173,174]

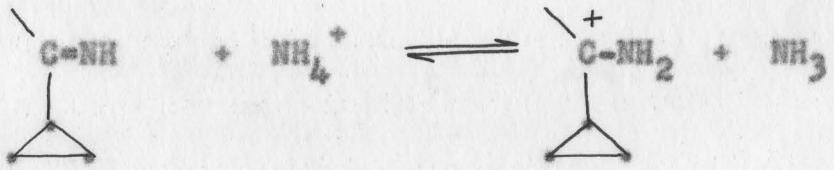
Apparently, while pyrrolines 98 and 99 resulted from rearrangement of the intermediate ketimines (see Chart VII), the isomeric intermediate ketimine (115) due to less steric hindrance was able



115

to cyclize as illustrated in Chart X. The reason for this facile cyclization is not immediately obvious. The possibility of ketone formation followed by cyclization was eliminated by the fact that no carbonyl function was observed in infrared spectra of the reaction mixture before hydrolysis, or before distillation of the hydrolyzed product. Also when the corresponding ketone (105), synthesized by a different method, was subjected to treatment of aqueous ammonium chloride for two days, no cyclized material was obtained, and the ketone was

recovered quantitatively. The possibility of normal acid-catalyzed cyclization by residual hydrochloric acid from the aqueous ammonium chloride was strengthened by the observation that the cyclized product was obtained upon hydrolysis of the magnesium complex with excess distilled water. The explanation for this facile cyclization may be associated with the electronic nature of the cyclopropyl group. That the three-membered ring has a system of weakly bound electrons similar in behavior to the π-electrons of ethylene has been well established.[175,176] Roberts[177] demonstrated that the cyclopropyl ring is more effective than a double bond in stabilizing a developing carbonium ion. Therefore, if the first step (reversible protonation) of the accepted mechanism[167] is as shown, the powerful +I effect of the cyclopropyl ring directly adjacent to



the developing carbonium ion would effect a stabilization causing a shift in the equilibrium to the right. Although Vingiello *et al.*[168] noted a general trend in reaction rates that indicated the second step is more

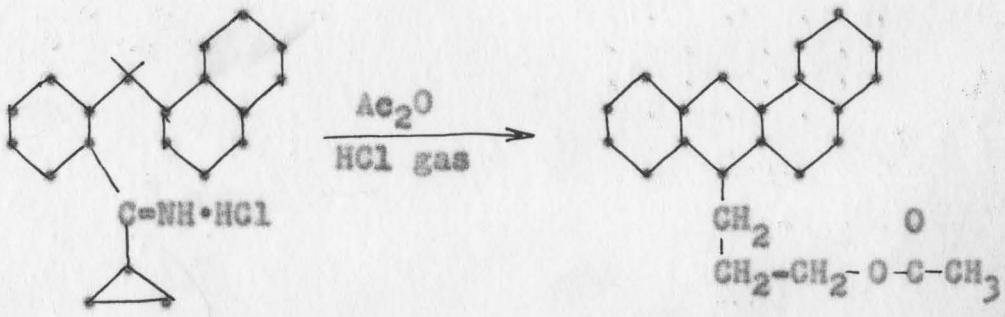
susceptible to the effects of substituents than is the first step, the unique electrical properties of the cyclopropyl group could quite conceivably effect a reversal of such a trend.

An alternative explanation for the facile cyclization could be that the Grignard reagent which was present in excess effected a base-catalyzed cyclization. To test the validity of a base-catalyzed cyclization, the corresponding ketone was treated with potassium hydroxide in quinoline. A yield of less than twenty percent of the desired 7-cyclopropylbenz[a]-anthracene (114) was obtained. Isolation of cyclized material indicated that base-catalysis for the ketimine cyclization was not unreasonable. While both acid- and base-catalysis appear feasible for this ring closure, the cyclization is so facile that it possibly needs no catalyst at all.

The intermediate ketimine (115) was isolated by hydrolyzing the magnesium complex with an equimolar amount of water. This extremely reactive ketimine could not be purified for elemental analysis since on recrystallization attempts either the alcohol present or the applied heat effected cyclization. Similar results were obtained in the case of the corresponding

ketimine hydrochloride. This crude hydrochloride salt was obtained from 115 by treating an ethereal solution of the ketimine with anhydrous hydrogen chloride gas.

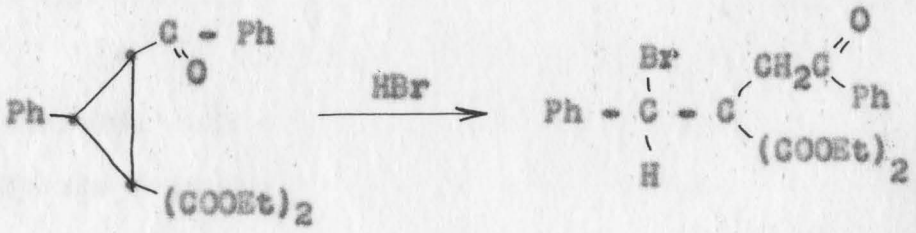
Since neither the free imine or the hydrochloride salt could be purified, the crude salt was treated with acetic anhydride saturated with anhydrous hydrogen chloride gas. This reaction resulted in fifty percent yield of 7-(3-acetoxypropyl)benz[a]anthracene (116). The structure was confirmed by elemental analysis, and



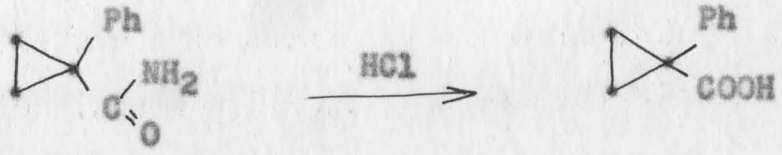
116

its infrared spectrum showed absorption in the ester region (see Appendix). The position of the acetoxy group was deduced from the known fact that electron withdrawing groups on the ring cause a counter-Markownikoff addition upon ring opening by strong acids.[178]

The cyclization of cyclopropyl 2-(1-naphthylmethyl)phenyl ketone (105) to 7-cyclopropylbenz[a]anthracene (see Chart X) required some extensive experimentation. Recent chemical literature is very confusing on the aspect of chemical action of various acids on the cyclopropane ring system. Kohler and Conant[114] reported that hydrobromic acid opened compound 117 to give compound 118 below. However, boiling concentrated hydrochloric acid caused no ring rupture whatsoever in the case of 1-phenylcyclopropane

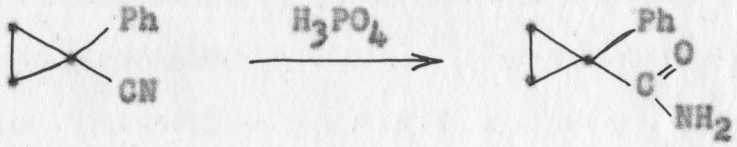


117 118



119 120

carboxamide (119).[179] Similarly, the same authors[179] report only hydrolysis of the cyano group to an amide function when 1-phenylcyclopropyl cyanide (121) was



121 119

heated in the presence of phosphoric acid while Davidson[180] reported formation of olefins from alkylcyclopropanes under similar treatment. Fuson[181] reported that cyclopropyl mesityl ketone upon treatment with a hydrobromic acid-acetic acid mixture yielded γ-bromobutyromesitylene, but if the ketone was treated with hydrobromic acid alone no ring rupture occurred.

It was therefore no surprise that neither a hydrobromic acid-acetic acid mixture nor phenyl acid phosphate resulted in an isolable product. Apparently some cyclization occurred since a normal benz[a]anthracene ultraviolet spectrum was obtained from the product in each case. When hydriodic acid was employed a product was obtained whose elemental analysis showed only carbon, hydrogen and iodine present but the product apparently was a mixture of ring ruptured material and normal cyclized product. A minute amount of 7-cyclopropylbenz[a]anthracene was isolated from this reaction.

Successful cyclization was effected by the previously mentioned potassium hydroxide and quinoline method. The method of Burger and Yost[182] using phosphorus pentoxide in toluene was quite successful. Both anhydrous hydrogen fluoride and anhydrous hydrogen fluoride in conjunction with benzene were successful cyclization media. When the benzene was not used extensive charring occurred during the reaction. The hydrogen fluoride reagent will be discussed more fully in the following section.

Once cyclized into the benz[a]anthracene system the cyclopropyl ring assumed a remarkable degree of unreactivity. This phenomenon is most likely due to the interation of the π electrons of the aromatic nucleus with those loosely bound "π-like" electrons[175] of the cyclopropyl group. This stability was established by the fact that 7-cyclopropylbenz[a]anthracene was recovered quantitatively from Raney nickel and platinum oxide hydrogenation attempts. Treatment with the following acid media - hydrobromic acid-acetic acid, hydriodic acid and glacial acetic acid - had no effect on the cyclized product while similar treatment of the corresponding ketone with the same acid systems resulted in unidentifiable mixtures.

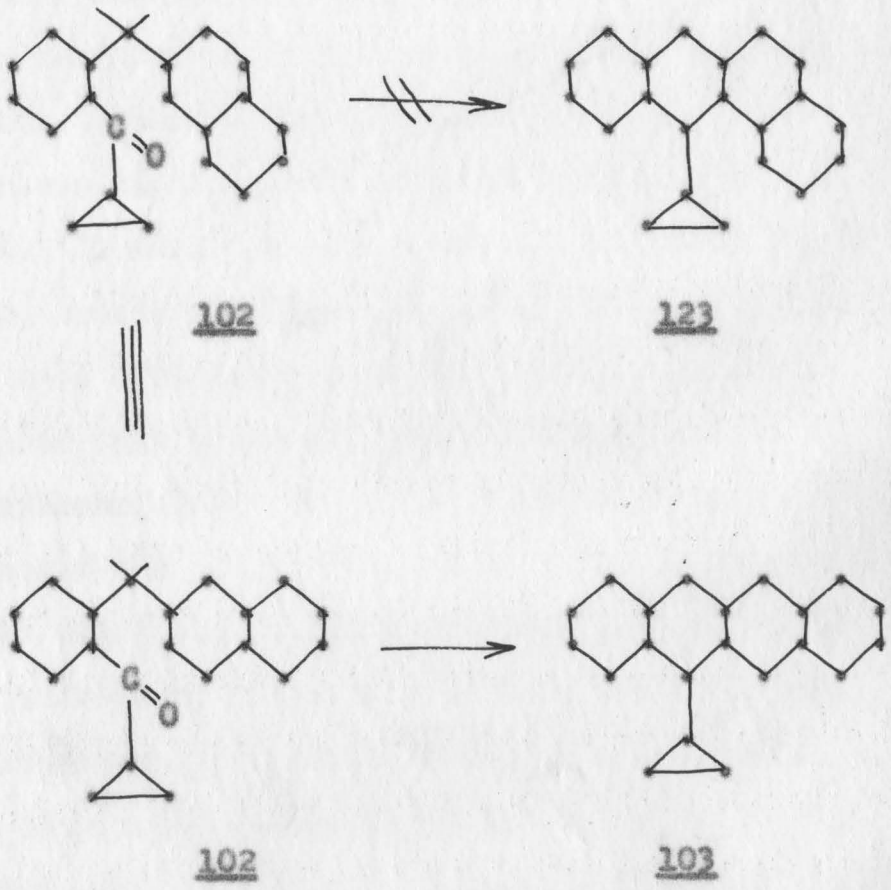
This striking stability of 7-cyclopropylbenz[a]-anthracene was further substantiated by polarographic analysis. Mason[183] observed a significant increase in the negative half-wave potential for 7-cyclopropyl-benz[a]anthracene over that for either unsubstituted benz[a]anthracene or 7-phenylbenz[a]anthracene. This higher potential is indicative of greater stability to polarographic reduction.

5. 5-Cyclopropylnaphthacene.

It was mentioned previously in Section B.5, Discussion of Results, that a minute amount of 5-cyclo-propylnaphthacene (103) was isolated along with the major product, 2-(2-Δ^1-pyrrolinyl)phenyl-2-naphthylmethane (99), as a result of the reaction between cyclopropyl cyanide and 2-(2-naphthylmethyl)phenylmagnesium bromide.

Treatment of cyclopropyl 2-(2-naphthylmethyl)-phenyl ketone (102) with the usual acid media gave no 12-cyclopropylbenz[a]anthracene (see Chart XI). Similar results as realized for cyclopropyl 2-(1-naphthylmethyl)-phenyl ketone (see previous section) were obtained in this case upon treatment with hydriodic acid, phenyl acid phosphate, and aqueous ammonium chloride. In addition, polyphosphoric acid and alumina were used unsuccessfully. The alumina method of cyclization described by Vingiello

CHART XI



102 123

102 103

and Borkovec[171] resulted in no isolable organic fraction. Apparently the cyclopropane system becomes too tightly bound to the alumina to be removed by elution.

Fisher-Hirschfelder-Taylor molecular models indicate that 12-cyclopropylbenz[a]anthracene (122) is sterically incapable of formation. The tertiary hydrogen of the cyclopropane ring appears to cause the most steric hindrance, although the methylene hydrogens on the other two carbons significantly contribute to the overall problem. It should be pointed out that newly acquired Dreiding models of 122 can be made easily. It does not appear that Dreiding models are reliable guides for this particular type of structures. Dreiding models of 12-phenylbenz[a]anthracene indicate completely free rotation of the phenyl ring which is contrary to all chemical data; the Dreiding model of 12-cyclohexylbenz[a]anthracene can easily be made while Fisher-Hirschfelder-Taylor models show that a cyclohexyl group cannot even approach the 12-position. Further, the Dreiding model of 7-(2-carboxyphenyl)benz[a]anthracene (123), which has been separated by Greenwood[184] into its optical isomers, exhibits free rotation. It therefore appears that, on the basis of Fisher-Hirschfelder-Taylor

models, 12-cyclopropylbenz[a]anthracene cannot be synthesized due to steric hindrance.

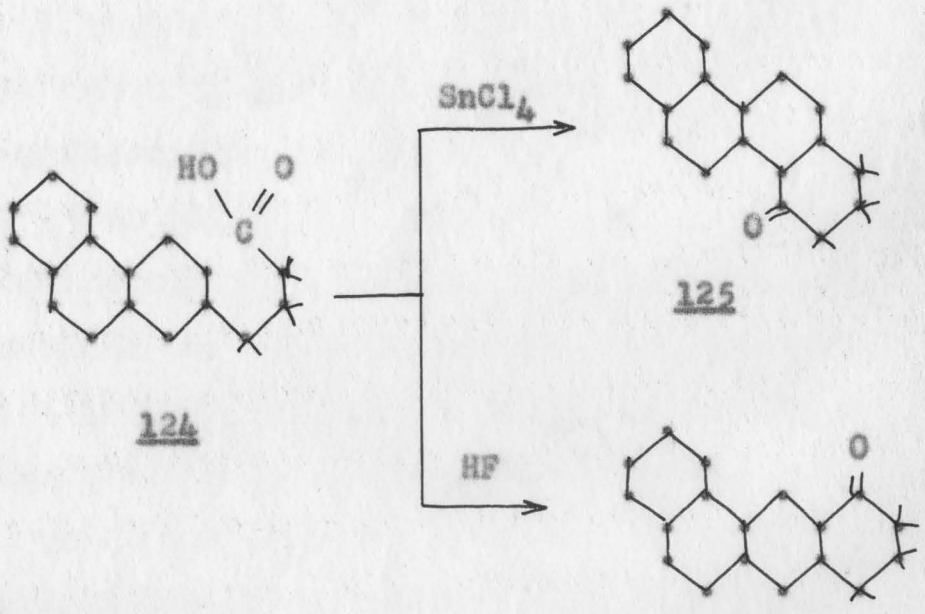
Chart XI illustrates the two possible positions for ring closure. Although the α-position is known to be relatively more reactive than the β-position,[185] steric hindrance could effect cyclization into the β-position. Vingiello and Borkovec[173] noted in the cyclization of certain hindered ketones the presence of an unidentifiable by-product which exhibited characteristic naphthacene properties.

Only a small amount of 5-cyclopropylnaphthacene had been obtained from the cyclization of the ketimine and none of the attempts to cyclize the ketone had proved successful. Since hydrogen fluoride was known to generally give a "clean" reaction product,[186] it was used as a cyclization catalyst in spite of the fact that it was known[187] to cause ring rupture in cyclopropane derivatives.

When hydrogen fluoride was added to ketone 102 in the usual manner,[186] immediate darkening of the reaction mixture occurred accompanied by precipitation. Along with some charred product, a small amount of 5-cyclopropylnaphthacene (103) was isolated. No

spectral evidence of a benz[a]anthracene system was found in the product.

Although the production of a naphthacene system here was not too surprising in view of the previous discussion on steric hindrance, the fact that no ring rupture occurred was unexpected. Fieser and Johnson[188] had previously demonstrated that while stannic chloride caused normal cyclization of γ-2-phenanthrylbutyric acid (124) into the α-position, hydrogen fluoride caused cyclization into the β-position in eighty percent yield.



124 125 126

In view of the poor although encouraging results obtained from hydrogen fluoride, it seemed that if the action of the hydrogen fluoride could be moderated, the charring or polymerization of the product could be reduced. Kilpatrick[189] observed that benzene in hydrogen fluoride does not undergo disproportionation, isomerization or polymerization as do a number of other aromatic substances. Anhydrous benzene therefore was chosen as a solvent to moderate this cyclization of ketone 102 (see Chart XI).

The use of this modification of the usual hydrogen fluoride cyclization on cyclopropyl 2-(2-naphthylmethyl)-phenyl ketone (102) resulted in near quantitative yield of 5-cyclopropylnaphthacene (103).

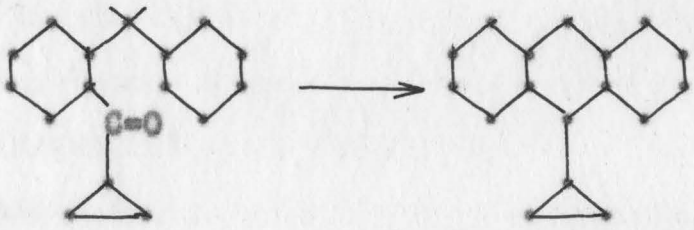
This high yield of product from cyclization into the less reactive β-position in the naphthyl group may be explained in the following manner. With protonation of benzene by hydrogen fluoride definitely established,[189] the resulting protonated species, a powerful acid, not only acts as the acid catalyst, but also may protonate the electron-rich α-position of the naphthyl group, thus effectively blocking it to further reaction. This occurrence, coupled with the steric hindrance effect,

apparently causes cyclization quantitatively into the β-position.

Attempts to prepare a 2,4,7-trinitrofluorenone molecular complex of both 5-cyclopropylnaphthacene and 7-cyclopropylbenz[a]anthracene by the Orchin method[190] failed.

6. 9-Cyclopropylanthracene.

Cyclopropyl 2-benzylphenyl ketone (106) was cyclized to 9-cyclopropylanthracene (127) by the Burger method[182] using phosphorus pentoxide in toluene. The



106 127

product, a low-melting solid, was crystallized with difficulty from methanol-ether. All other usual solvents and solvent-mixtures failed to effect crystallization. The structure of 9-cyclopropylanthracene was confirmed by elemental analysis and its ultraviolet spectrum which indicated the presence of the anthracene ring system.

D. Spectral Interpretations.

1. Infrared spectra.

All infrared absorption spectra were recorded on a Beckman IR-5 Infrared Spectrophotometer.

The infrared spectra of the three new dimethylaminophenyl ketones show a peak in the region of 6.2-6.3 microns which masks the carbonyl absorption. In the case of 2-(1-naphthylmethyl)-2'-dimethylaminobenzophenone the carbonyl peak is completely masked. This is a special case, however; the steric effect of the bulky dimethylamino group ortho to the carbonyl group may quite likely cause such a phenomenon. This strong absorption at approximately 6.2 microns has been observed in similar compounds (see Sadtler Infrared Spectra Nos. 6 and 12435 for dimethylaniline and N,N-dimethyl-p-tert-butylaniline, respectively).

The two pyrroline derivatives exhibited three adjacent strong bands in the C-H absorption region. These bands could be superimposed on each other and were quite distinctive. These peaks, occurring at 3.3, 3.4 and 3.5 microns, are also noted in the Sadtler Infrared Spectra No. 2966 for 1,2,5-trimethylpyrroline.

The presence of a cyclopropyl group in an organic molecule is difficult to establish by chemical means. By use of infrared absorption spectra, Derfer[191] has shown

that a moderate to strong band in the 1030-1000 cm^{-1} region (most generally at 9.9 microns) is useful in identifying this ring structure. Bellamy[192] attributed this band to ring deformation modes.

Weitkamp[193] has recently reported that identification of the cyclopropane structure exclusively by infrared analysis is not possible. He demonstrated that the position of the characteristic bands in forty-two cyclopropyl derivatives is so influenced by substitution that they cannot be used for identification.

In spite of the danger involved in depending on infrared bands for identification of the cyclopropyl group, it seems that if the bands are present that one could safely assume the presence of the group.

The following new cyclopropyl derivatives exhibited a band at the indicated wavelength which in each case is well within the 1030-1000 cm^{-1} region described by Derfer.[192]

Cyclopropyl Derivative	Wavelength, in microns
Cyclopropyl 2-(1-naphthylmethyl)phenyl ketone (105)	9.7
Cyclopropyl 2-(2-naphthylmethyl)phenyl ketone (102)	9.7
Cyclopropyl 2-benzylphenyl ketone (106) . . .	9.7
7-Cyclopropylbenz[a]anthracene (114)	9.9
5-Cyclopropylnaphthacene (103)	9.9
9-Cyclopropylanthracene (127)	9.9

2. Ultraviolet spectra.

All ultraviolet absorption spectra were recorded on a Beckman DK-2A Spectrophotometer.

In contrast to absorption of infrared radiation, which is a result of molecular vibrations, the absorption of ultraviolet radiation results from electronic excitation. It is well known that increasing conjugation causes a shift of the absorption bands to longer wavelengths. Steric hindrance, on the other hand, produces a hypsochromic shift which is quite often accompanied by a decrease in the intensity of the band.[194] Usually steric effects result from interference with coplanarity

of a substituent and an aromatic nucleus to which it is attached. Some molecular distortions produce a spectral effect exactly opposite to that generally associated with steric hindrance. This effect may arise from strain in the bonds of the entire aromatic system rather than from disruption of the coplanarity of two groups.[194] Jones[195] reported that in more highly condensed aromatic systems this effect is exhibited by some benz[a]anthracenes containing a saturated ring. Delia[196] reported a considerable decrease in intensity of the absorption bands in 7-cyclohexylbenz[a]anthracene.

7-Cyclopropylbenz[a]anthracene exhibited an almost identical absorption spectrum to that of Delia's cyclohexyl compound. It appears then that the flattened peak in the spectra of 7-cyclopropylbenz[a]anthracene should indeed be expected. The possibility of π electron interaction between the two ring systems could be the cause of this decrease in intensity. A second likely possible explanation could be the strain the saturated ring puts on the adjacent bonds in the aromatic nucleus (as noted in the Fisher-Hirschfelder-Taylor models).

The absorption maxima for 5-cyclopropylnaphthacene coincide in relative intensity and approximate position with the maxima exhibited[209] by naphthacene.

The ultraviolet spectrum for a naphthacene compound is quite distinctive; there are four sharp peaks in the 390 to 500 millimicron region. No flattened curve was noted in the case of naphthacene derivative as was noted in the case of the benz[a]anthracene derivative. This may be due to difference in the region of maximum absorption for the two derivatives.

Compound	Absorption Maxima, in millimicrons			
Benz[a]anthracene		277	287	
7-Cyclopropylbenz[a]anthracene . .		282.5	292.5	
7-Cyclohexylbenz[a]anthracene . . .		281	291	
Naphthacene	393	415	441	471
5-Cyclopropylnaphthacene	397	423	450	481

EXPERIMENTAL

EXPERIMENTAL [a,b]

2-Bromotoluene.

A solution of 162 g. (1.5 moles) of o-toluidine in 880 ml. of 40% hydrobromic acid in a 4000 ml. Erlenmeyer flask was cooled to 10° and diazotized with 116 g. (1.7 moles) of sodium nitrite added in 5 g. portions. After each addition the flask was stoppered and shaken until all the red fumes were absorbed. The temperature of the mixture was kept below 10° by an ice-salt bath. After the diazotization was complete, 5 g. of powdered copper was added, a reflux condenser attached to the flask and the contents carefully heated. At the first sign of reaction the flask was cooled. Nitrogen was evolved very vigorously. After the evolution of nitrogen subsided the flask was heated on a steam bath for 30 min. One liter of water was added and the solution was steam distilled until 2 l. of distillate was collected. The distillate was made alkaline to litmus with sodium

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a All melting points were recorded on either a Thomas-Hoover or Mel-Temp capillary melting point apparatus and are corrected.

b All elemental analyses were performed as noted by Geller Laboratories, Bardonia, New York, except those by Galbraith Laboratories, Knoxville, Tennessee, which are marked by an asterisk.

hydroxide and the red organic layer which formed was separated, washed once with an equal volume of concentrated sulfuric acid, twice with equal volumes of water and finally dried over calcium chloride. The crude 2-bromotoluene was filtered and distilled at atmospheric pressure. The product was collected as a pale yellow liquid at 177-181°, (lit.[128] 178-181°); yield 106 g. (41%).

Five additional runs were made using the same procedure. The weight of o-toluidine and yield found in each case were: 162 g. (1.5 moles), 69 g. (27%); 54 g. (0.5 mole) (repeated four times), 32 g. (37%), 30 g. (35%), 31 g. (36%), and 32 g. (37%).

2-Bromobenzaldehyde (61).

In a 500 ml. round-bottomed flask equipped with a mechanical stirrer, reflux condenser and a separatory funnel was placed 171 g. (1.0 mole) of 2-bromotoluene. When this had been heated to 130° with stirring and irradiated with ultraviolet light (3360 Å), 160 g. (1.0 mole) of bromine was added dropwise. Upon completion of this addition, the temperature of the contents of the flask was raised to 165° and a second mole of bromine was added dropwise. The mixture was

heated for an additional 45 min., poured into a 2 l. round-bottomed flask containing 150 g. of calcium carbonate and 500 ml. of water and heated under reflux for 9 hrs. The mixture was then steam distilled and a nearly colorless oil settled to the bottom of the distillate. The aqueous layer was separated, extracted with ether and the extract combined with the oil. The ethereal solution was then dried over anhydrous magnesium sulfate, filtered, concentrated and distilled under reduced pressure. The product was collected as a slightly yellow oil at 100-104° (5 mm.), (lit.[197] 118-119° [12 mm.]); yield 86 g. (47%).

An additional run was made using the same quantities of reagents. The product obtained weighed 53 g. (29%).

2-Bromobenzyl Bromide (64).

A mixture of 370 g. (2.2 moles) of 2-bromotoluene and 8.8 g. of benzoyl peroxide was dissolved in 640 ml. of anhydrous benzene in a 5 l. 3-necked flask equipped with a mechanical stirrer, reflux condenser and 24/40 to 45/50 enlarging adapter. This solution was heated to vigorous reflux and a mixture of 384 g. (2.2 moles) of N-bromosuccinimide and 8.8 g. of benzoyl peroxide

was added through the adapter as fast as foaming would allow. After the addition was complete and the foaming had subsided, the reaction mixture was cooled in an ice bath and the precipitated succinimide was filtered and washed with anhydrous benzene. The solution was concentrated and the crude product was distilled under reduced pressure. The product was collected as a colorless liquid at 111-115° (8 mm.), (lit.[198] 127-133° [15 mm.]); yield 455 g. (84%).

Two additional runs were made using the same procedure. The weight of 2-bromotoluene and yield of the product in each case were: 86 g. (0.5 mole), 101 g. (81%); 86 g. (0.5 mole), 74 g. (54%).

2-Bromodiphenylmethane (63).

A. A Grignard reagent was prepared from 218 g. (1.4 moles) of bromobenzene and 33.9 g. (1.4 g. atoms) of magnesium turnings in 200 ml. of anhydrous ether in a 1 l. 3-necked flask equipped with a mechanical stirrer, reflux condenser and separatory funnel. A solution of 128 g. (0.7 mole) of 2-bromobenzaldehyde in 125 ml. of anhydrous ether was added with stirring over a period of 3.5 hrs. and the resultant milky solution was heated under reflux for 2 hrs. The mixture was hydrolyzed with

an equivalent amount of a 20% ammonium chloride solution and the ether layer decanted and dried overnight over anhydrous magnesium sulfate. The magnesium sulfate was removed by filtration and the ether was removed by distillation. The resultant oil, dissolved in glacial acetic acid, was placed in a 2 l. 3-necked flask equipped with a mechanical stirrer, reflux condenser and a separatory funnel. To this flask was added 24.8 g. (0.8 g. atom) of red phosphorus, 24.8 g. (0.2 g. atom) of iodine and a total of 1.4 l. of glacial acetic acid and the contents heated under reflux for 26 hrs. The resultant dark red solution was filtered while hot, the filtrate poured over twice its volume of ice, then neutralized with 20% sodium carbonate solution and finally extracted with ether. The ether extracts were washed first with 10% sodium hydroxide then with water. The ether layer was then dried overnight over anhydrous magnesium sulfate, the solution was filtered and the filtrate concentrated and distilled. The product was collected at 181.5-185° (22 mm.), (lit.[199] 180-183° [22 mm.]); yield 120 g. (69%).

An additional run was made using the same procedure and quantities of reactants. The product weighed 72 g. (33%).

B. A Grignard reagent was prepared from 47 g. (0.3 mole) of bromobenzene and 7.3 g. (0.3 g. atom) of magnesium turnings in 150 ml. of anhydrous ether in a 500 ml. 3-necked flask equipped with a mechanical stirrer, take-off condenser and separatory funnel. After most of the magnesium had reacted, the ether was removed and replaced with anhydrous benzene. Then 37 g. (0.15 mole) of 2-bromobenzyl bromide in 75 ml. of anhydrous benzene was added as fast as foaming would allow. The solvent was removed until the boiling point of the solution reached 75°, and the mixture was heated for 2 hrs. The mixture was hydrolyzed with 75 ml. of 20% hydrochloric acid. The benzene layer was separated from the aqueous layer which was extracted with benzene and the combined benzene layers dried over anhydrous magnesium sulfate. The dried solution was filtered, concentrated and distilled under reduced pressure. The product was collected as a colorless oil at 182-188° (22-23 mm.), (lit.[199] 180-183° [22 mm.]); yield 16 g. (42%).

2-(1-Naphthylmethyl)bromobenzene (65).

A Grignard reagent was prepared from 83 g. (0.4 mole) of 1-bromonaphthalene and 9.7 g. (0.4 g. atom) of magnesium turnings in 250 ml. of anhydrous ether

in a 500 ml. 3-necked flask equipped with a magnetic stirrer, take-off condenser and separatory funnel. After most of the magnesium had reacted, most of the ether was removed and replaced by anhydrous toluene. Then 64 g. (0.26 mole) of 2-bromobenzyl bromide in 100 ml. of anhydrous toluene was added as fast as foaming would allow. The solvent was removed until the boiling point of the solution reached 80°, and the mixture was heated for 2.5 hrs. The mixture was hydrolyzed with 0.4 mole of hydrochloric acid. The toluene layer was separated from the aqueous layer which was extracted with benzene and the combined organic layers concentrated. The crude product was heated under reduced pressure in a round-bottomed flask equipped with a Hopkins condenser. A by-product which sublimed was collected on the cold finger of the condenser. The residual oil was distilled under reduced pressure. The product was collected as a viscous yellow oil at 177-182° (1.5 mm.), (lit.[200] 168-178° [0.25 mm.]); yield 76 g. (74%).

Two additional runs were made using the same procedure. The weight of 2-bromobenzyl bromide used and the yield in each case were: 64 g. (0.26 mole), 49 g. (41%); 128 g. (0.52 mole), 105 g. (63%).

2-Bromonaphthalene (69).

A. A mixture of 100 g. (0.7 mole) of technical grade 2-naphthylamine, 280 ml. of concentrated hydrochloric acid, and 1340 ml. of water in a 4 l. beaker was treated at 0-5° with 350 ml. of a 20% sodium nitrite solution. To the resulting red solution of the diazonium salt was added with stirring a cold solution of mercuric bromide formed by treating 114 g. (0.36 mole) of mercuric nitrate with 166 g. (1.6 moles) of sodium bromide in a total volume of 500 ml. of water. The precipitated yellow complex was removed by filtration, washed with water, then acetone, and air dried for four days. The solid was mixed with 300 g. of sodium bromide and this mixture was added portionwise to a 3-necked 1 l. flask which was heated to 110-120° (pyrometer reading) and equipped with a reflux condenser. Vigorous evolution of gas followed each portionwise addition of the salt mixture. After decomposition was complete, the reaction mixture was extracted with benzene (5 l.). Removal of solvent followed by vacuum distillation of the residual oil gave a product boiling at 116° (4 mm.). The oil solidified on standing. Further purification was effected by dissolving the product in n-hexane and

passing this solution over a column packed with 2 in. of neutral alumina.[c] The eluant was cooled to 0° and the resulting white solid filtered, m. p. 54-56°, (lit.[134] 55-56°); yield 64 g. (44%).

Three additional runs were made and combined before decomposition of the yellow complex. Starting in each case with the same quantities, the reaction yielded 130 g. (30%).

B. A solution of 446 g. (2.0 moles) of 2-amino-1-naphthalenesulfonic acid in 3600 ml. of aqueous sodium hydroxide (2.05 moles) was prepared in a 2 gallon jar fitted with a mechanical stirrer. To this was added with stirring a solution of 138 g. (2.0 moles) of sodium nitrite in 500 ml. of water. The resulting solution was filtered.

Meanwhile, 1 l. of concentrated hydrochloric acid and 450 g. of crushed ice were placed in a 5 gallon can which was cooled in an ice bath and fitted with a mechanical stirrer. The filtered solution from above was then added dropwise with stirring while the

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c All chromatography columns used by this investigator were 16 mm. in diameter. The alumina used was Fisher's Basic, Acidic, or Neutral Alumina, Brockman Activity 1, 80-200 mesh.

temperature was maintained below 5° by the addition of ice. Upon completion of the diazotization, the yellow precipitate was filtered using a vacuum.

A suspension of cuprous bromide in 300 ml. of 48% hydrobromic acid and 800 ml. of water was prepared. The cuprous bromide was prepared as needed by the method described by Hartwell.[210] The damp cake of the diazonium salt was added portionwise and stirred into the previously prepared suspension in a 5 gallon can fitted with a mechanical stirrer. After the vigorous evolution of nitrogen had subsided, the mixture was heated on a steam bath until nearly all of the material had dissolved and was then filtered hot through a large Buchner funnel. The filtrate was poured into a 4 l. beaker and 450 g. of potassium chloride was added with stirring. The resulting slurry was allowed to cool to room temperature, filtered with suction, washed with 1 l. of a 20% solution of potassium chloride and then with water until the solid was pink. The 2-bromo-1-naphthalenesulfonic acid was air dried and placed in a 5 l. round-bottomed flask.

A solution prepared from 800 ml. of concentrated sulfuric acid and 800 g. of ice was added with

intermittent shaking. A reflux condenser was attached to the flask and the mixture heated under reflux for 15 hrs. After allowing the solution to cool to room temperature, it was poured onto 200 g. of ice. The chilled solution was then extracted with 5 l. of benzene. The dark organic layer was separated, filtered and concentrated. The residual oil was distilled under reduced pressure. The product was collected as a slightly yellow oil, which solidified on standing, at 115-121° (7 mm.), (lit.[134] 103-104° [4 mm.]); yield 112 g. (27%).

2-(2-Naphthylmethyl)bromobenzene (66).

A Grignard reagent was prepared from 83 g. (0.4 mole) of 2-bromonaphthalene and 9.9 g. (0.41 g. atom) of magnesium turnings in 250 ml. of anhydrous ether in a 500 ml. 3-necked flask equipped with a magnetic stirrer, reflux condenser and separatory funnel. A solution of 56 g. (0.3 mole) of 2-bromobenzaldehyde in 100 ml. of anhydrous ether was added dropwise to the Grignard reagent, and the mixture refluxed for 2 hrs. The mixture was cooled and decomposed with 200 ml. of 10% hydrochloric acid. The organic layer was separated, washed with water and dried

over anhydrous magnesium sulfate. This solution was then added dropwise to a slurry[133] of 40 g. (0.3 mole) of aluminum chloride and 5.7 g. (0.15 mole) of lithium aluminum hydride. The mixture was heated under reflux for 1 hr. following the addition. Excess lithium aluminum hydride - aluminum chloride was destroyed by adding ethyl acetate. The resulting mixture was poured into 1 l. of 20% sulfuric acid, the ether layer separated, washed once with 10% sodium hydroxide, twice with water, dried over calcium chloride and then concentrated. The product was distilled and collected as a viscous yellow oil at 194-200° (0.8 mm.), (lit.[201] 230-240° [2 mm.]); yield 52 g. (58%).

1-Bromo-2-methylnaphthalene (74).

A solution of 142 g. (1.0 mole) of commercial 2-methylnaphthalene in 300 ml. of carbon tetrachloride with a small crystal of iodine and 0.03 g. of iron powder was placed in a 1 l. 3-necked flask equipped with a mechanical stirrer, reflux condenser and a separatory funnel. The mixture was cooled to below 0° and the flask was covered with a towel to exclude light. While an ice-salt bath was used to maintain the pot

temperature around -4° a solution of 176 g. (1.1 moles) of bromine in 300 ml. of carbon tetrachloride was added dropwise over a 2 hr. period. The solution was stirred overnight and then allowed to warm to room temperature. The solution was washed with water, then with 10% sodium hydroxide, again with water, and then dried over calcium chloride. The solution was filtered, concentrated and distilled at reduced pressure. The product was collected as a slightly yellow oil at 118° (0.5 mm.), (lit.[202] 112-117° [1 mm.]); yield 187 g. (85%).

An additional run was made using the same amount of starting materials. The product weighed 174 g. (79%).

1-Bromo-2-bromomethylnaphthalene (75).

In a 1 l. 3-necked flask, equipped with a mechanical stirrer, reflux condenser and a 24/40 to 45/50 enlarging adapter, was placed 174 g. (0.78 mole) of 1-bromo-2-methylnaphthalene, 350 g. of carbon tetrachloride and 2.0 g. of benzoyl peroxide. To this was added in portions 150 g. (0.82 mole) of N-bromo-succinimide and when the reaction had subsided the mixture was heated under reflux for an additional 2 hrs. To the hot solution was added 200 ml. of carbon

tetrachloride and the entire mixture filtered with suction. The solid succinimide was washed with 100 ml. of hot carbon tetrachloride. The organic extracts were combined and the solvent removed using an aspirator. The resulting tan solid was filtered and dried, m. p. 97-101°, (lit.[203] 103.5-105.5°); yield 148 g. (63%).

An additional run was made using 187 g. (0.85 mole) of starting material. The product weighed 154 g. (61%).

2-Benzyl-1-bromonaphthalene (76).

A Grignard reagent was prepared from 47 g. (0.3 mole) of bromobenzene and 7.2 g. (0.3 g. atom) of magnesium turnings in 100 ml. of anhydrous ether in a 500 ml. 3-necked flask equipped with a magnetic stirrer, take-off condenser and separatory funnel. When most of the magnesium had reacted, the ether was removed and replaced with anhydrous benzene until the boiling point of the solution reached 75°. Then 50 g. (0.16 mole) of 1-bromo-2-bromomethylnaphthalene dissolved in 200 ml. of anhydrous benzene was added rapidly. The resulting yellow-brown mixture was heated under reflux for 20 hrs. The mixture was cooled and hydrolyzed with 200 ml. of water and 40 ml. of concentrated hydrochloric acid.

The organic layer was decanted and the aqueous layer extracted with ether. The organic portions were combined, dried over calcium chloride, filtered and concentrated. The crude product was heated under reduced pressure in a round-bottomed flask equipped with a Hopkins condenser. A by-product which sublimed was collected on the cold finger of the condenser. The residual oil was distilled under reduced pressure. The product was collected as a clear liquid at 165-171° (0.5 mm.), (lit.[204] 136-138° [10^{-4} mm.]); yield 29 g. (61%).

Two additional runs were made using the same procedure. The weight of 1-bromo-2-bromomethylnaphthalene and the yield obtained in each case were: 147 g. (0.49 mole), 64 g. (44%); 147 g. (0.49 mole), 72 g. (49%).

2-Chlorodiphenylmethane (78).

A solution of 100 g. (0.62 mole) of commercial 2-chlorobenzyl chloride dissolved in 200 ml. of benzene was added slowly to a 1 l. 3-necked flask which was equipped with a magnetic stirrer, reflux condenser and separatory funnel, and which contained 600 ml. of anhydrous benzene and 8.0 g. (0.06 mole) of anhydrous

aluminum chloride. The period of addition was 90 min. and the initial temperature of the flask's contents was 10°. The reaction was allowed to continue for 30 min. after the completion of the addition. The reaction was stopped by pouring the solution into 3 l. of water. The benzene layer was decanted from the water, washed with water, dried over calcium chloride and concentrated. The crude product was distilled under reduced pressure. The product, a clear liquid, was collected at 132-139° (5 mm.), (lit.[166] 138-142° [5 mm.]); yield 76 g. (61%).

Three additional runs were made using the same procedure. Twice the same amounts were used giving 64 g. (51%) and 59 g. (47%); once the quantities of reagents were doubled giving 140 g. (56%).

2-(1-Naphthylmethyl)chlorobenzene (80).

A Grignard reagent was prepared from 207 g. (1.0 mole) of 1-bromonaphthalene and 24 g. (1.0 g. atom) of magnesium turnings in 400 ml. of anhydrous ether in a 2 l. 3-necked flask equipped with a mechanical stirrer, take-off condenser and separatory funnel. When the reaction had subsided, a 9 ml. aliquot was removed and by the Gilman method of titration the percentage Grignard

reagent formation was determined to be 59%. Anhydrous toluene (400 ml.) was added and the ether removed by means of the take-off condenser until the boiling point of the solution reached 75°. A solution of 97 g. (0.6 mole) of 2-chlorobenzyl chloride in 230 ml. of anhydrous toluene was added to the Grignard reagent as fast as foaming would allow. The mixture was then heated under reflux for 2 hrs. The solution was hydrolyzed with an equivalent amount of 20% hydrochloric acid. The two layers were separated and the organic layer dried over anhydrous magnesium sulfate, filtered and concentrated. The crude product was heated under reduced pressure in a round-bottomed flask equipped with a Hopkins condenser. A by-product which sublimed was collected on the cold finger of the condenser. The oil was then distilled under reduced pressure. The product was collected as a clear yellow oil at 183-199° (2 mm.), (lit.[205] 203-204° [3 mm.]); yield 100 g. (66%).

Two additional runs were made using the same procedure except that 1 mole quantities of both the benzyl chloride and the bromo compounds were used. The product weighed 92 g. (36%) and 122 g. (50%).

2-Cyanodiphenylmethane (79).

A mixture of 131 g. (0.64 mole) of 2-chlorodiphenylmethane, 62 g. (0.7 mole) of cuprous cyanide, 2 g. of anhydrous cupric sulfate and 42 ml. of anhydrous pyridine was placed in a 500 ml. round-bottomed flask. The mixture was heated for 25 hrs. in a Wood's metal bath maintained at a temperature of 255-270° (pyrometer reading). The solvent was removed by distillation and collected in a Barrett tube placed between the flask and its attached reflux condenser. The mixture was then crudely distilled using a von Braun distilling head. This distillate was then redistilled and the product collected as a clear oil at 156-157° (4 mm.), (lit.[166] 160-164° [4 mm.]); yield 75 g. (61%).

Three additional runs were made using the same procedure. The amount of chloro compound and the yield in each case were: 131 g. (0.64 mole), 70 g. (57%); 100 g. (0.05 mole), 59 g. (61%); 131 g. (0.64 mole), 70 g. (57%).

2-(1-Naphthylmethyl)benzonitrile (81).

A mixture of 90 g. (0.36 mole) of 2-(1-naphthylmethyl)chlorobenzene, 48 g. (0.54 mole) of cuprous

cyanide, 2 g. of anhydrous cupric sulfate and 50 ml. of anhydrous pyridine was placed in a 250 ml. round-bottomed flask. The mixture was heated for 20 hrs. in a Wood's metal bath maintained at 270-280° (pyrometer reading). The solvent was removed by distillation and collected in a Barrett tube placed between the flask and its attached reflux condenser. The mixture was then crudely distilled using a von Braun distilling head. This distillate was then redistilled and the product collected as a clear oil at 188-191° (2-3 mm.), (lit.[138] 200-204° [2 mm.]); yield 70 g. (81%).

Two additional runs were made using the same procedure. The amount of chloro compound and the yield in each case were: 90 g. (0.36 mole), 63 g. (73%); 99 g. (0.39 mole), 53 g. (56%).

2-Benzyl-1-cyanonaphthalene (77).

In a 250 ml. round-bottomed flask were combined 60 g. (0.20 mole) of 2-benzyl-1-bromonaphthalene, 29 g. (0.33 mole) of cuprous cyanide, 30 ml. of anhydrous pyridine and a few crystals of anhydrous cupric sulfate. The mixture was refluxed for 28 hrs. in a Wood's metal bath maintained at 270-280°. The excess pyridine was

removed by inserting a Barrett tube between the flask and the condenser. A von Braun distilling head was then attached to the flask and the mixture crudely distilled at reduced pressure. The crude product was then redistilled. The product was collected as a slightly yellow oil at 181-186° (1.0 mm.); yield 34 g. (70%).

The oil solidified on standing, and was recrystallized from 95% ethanol as white needles, m. p. 76-77°.

Anal.: Calcd. for $C_{18}H_{13}N$: C, 88.86; H, 5.38; N, 5.76. Found: C, 88.83; H, 5.48; N, 5.62.

2-Bromoaniline (84).

A. A solution of 20 g. (0.10 mole) of 2-nitrobromobenzene in 200 ml. of benzene was placed in a 500 ml. 3-necked flask equipped with a mechanical stirrer, reflux condenser and separatory funnel. The solution was heated almost to boiling on a steam bath. Activated iron (prepared by slowly adding 10 ml. of concentrated hydrochloric acid to 50 g. [0.9 mole] of granulated iron and the resulting mixture thoroughly air-dried) was added while maintaining vigorous stirring and refluxing. After 0.5 hr., 4 ml. of water was added to the reaction mixture; thereafter small quantities

of water were added so that at the end of 8 hrs. a total of 20 ml. had been added. At the completion of the addition of the water the mixture was refluxed one more hour. The clear benzene layer was decanted from the excess iron and treated with hydrochloric acid to obtain the amine hydrochloride as a white solid; yield 20 g. (96%). The hydrochloride salt (106 g.) was dissolved in 1.5 l. of water and placed in a 2 l. round-bottomed flask equipped with a magnetic stirrer and reflux condenser. The flask was placed in an ice bath and to it was added slowly an excess amount of 50% sodium hydroxide. Fine tan crystals separated and were filtered and dried overnight on an air aspirator, m. p. 30-31°, (lit.[206] 31-31.5°); yield 86 g. (98%).

Five additional runs were made using the same procedure. The amounts of nitro compound and yield of hydrochloride salt were: 10 g. (0.05 mole), 9.5 g. (91%); 20 g. (0.1 mole), 18 g. (87%); 20 g. (0.1 mole), 15 g. (73%); 41 g. (0.2 mole), 10 g. (24%); 50 g. (0.25 mole), no product due to inability to make good activated iron in large quantities.

B. A mixture of 228 g. (1.1 moles) or 2-nitrobromobenzene, 360 g. of mossy zinc and 700 ml. of water in

a 5 l. flask equipped with a reflux condenser was heated almost to boiling. Concentrated hydrochloric acid (550 ml.) was added dropwise to the hot mixture which was refluxed for 2 hrs. following the addition and then made strongly alkaline with 550 ml. of 50% sodium hydroxide. The alkaline mixture was steam distilled until 4 l. of distillate was collected. The distillate was extracted with ether and the ether extract was dried over anhydrous magnesium sulfate. The ethereal solution was filtered, concentrated and distilled under reduced pressure. The product was obtained as a yellow oil at 101-107° (13 mm.), (lit.[207] 138-141° [48-53 mm.]); yield 106 g. (55%).

2-Bromodimethylaniline (86).

To a mixture of 104 g. (0.06 mole) of 2-bromoaniline and 100 ml. of water contained in a 1 l. 3-necked flask equipped with a mechanical stirrer, separatory funnel and reflux condenser was added three equivalents (231 g.) of dimethyl sulfate. One equivalent was added with stirring and the mixture was allowed to stir until homogeneity was obtained. The mixture was then carefully neutralized with 25% sodium hydroxide, allowed to cool and then

treated with the second equivalent of methyl sulfate. The neutralization process was repeated using a slight excess (5 ml.) of base. Finally the third equivalent of methyl sulfate was added and the mixture was allowed to stand for one hour. The mixture was then extracted with ether, and the ether extract dried over anhydrous magnesium sulfate. The ethereal solution was filtered, concentrated and distilled at reduced pressure. The product was obtained as a pale yellow oil at 104-109° (13 mm.), (lit.[146] 100-101° [12 mm.]); yield 89 g. (73%).

An additional run was made using 0.5 mole of amine but upon distillation of product extensive decomposition was observed and no product was obtained.

3-Bromoaniline (85).

A mixture of 198 g. (0.98 mole) of 3-nitrobromobenzene, 360 g. of mossy zinc and 700 ml. of water in a 5 l. flask equipped with a reflux condenser was heated almost to boiling. Concentrated hydrochloric acid (500 ml.) was added dropwise to the boiling mixture which was refluxed for 2 hrs. following the addition and then made strongly alkaline with 550 ml. of 50%

sodium hydroxide. The alkaline mixture was steam distilled until 4.5 l. of distillate was collected. The distillate was extracted with ether and the ether extract was dried over anhydrous magnesium sulfate. The ethereal solution was filtered, concentrated and distilled under reduced pressure. The product was obtained as a pale yellow oil at 122-127° (12 mm.), (lit.[145] 130° [12 mm.]); yield 100 g. (59%).

An additional run was made using 200 g. (0.99 mole) and 73 g. (44%) of the desired product was obtained.

3-Bromodimethylaniline (87).

To a mixture of 98 g. (0.57 mole) of 3-bromoaniline and 100 ml. of water contained in a 1 l. 3-necked flask equipped with a mechanical stirrer, separatory funnel and reflux condenser was added three equivalents (219 g.) of methyl sulfate. One equivalent was added with stirring and the mixture was allowed to stand until homogeneity was obtained. The mixture was then carefully neutralized with 25% sodium hydroxide, allowed to cool and then treated with the second eauivalent of methyl sulfate. The neutralization process was repeated using a slight excess (5 ml.) of base. Finally the third

equivalent of methyl sulfate was added and the mixture was allowed to stand for one hour. The alkaline mixture was then extracted with ether and the ether extract dried over anhydrous magnesium sulfate. The ethereal solution was filtered, concentrated and distilled at reduced pressure. The product was obtained as a yellow oil at 110-112° (5 mm.), (lit.[146] 118-119° [8 mm.]); yield 84 g. (74%).

An additional run was made using 70 g. (0.4 mole) and 34 g. (42%) of the desired product was obtained.

2-Benzyl-4'-dimethylaminobenzophenone (90).

A solution of 8 g. (0.07 mole) of ethyl bromide in 50 ml. of anhydrous ether was added to 1.3 g. (0.05 g. atom) of magnesium turnings in a 500 ml. 3-necked flask equipped with a magnetic stirrer, reflux condenser and separatory funnel. After the reaction had continued for 5 min., 12.5 g. (0.06 mole) of p-bromodimethylaniline in 150 ml. of warm anhydrous ether was added. The mixture was warmed gently and a vigorous reaction took place. When the reaction had subsided, 4.0 g. (0.02 mole) of 2-benzylbenzonitrile in 80 ml. of anhydrous ether was added. The mixture was refluxed

for 22 hrs., then 75 ml. of anhydrous toluene was added and the heating continued for an additional 17 hrs. The mixture was hydrolyzed with 50 ml. of dilute hydrochloric acid and extracted with benzene. The organic extract was concentrated and the resulting red oil distilled. The product was collected at 269-271° (3 mm.) as a yellow oil which solidified as a glassy mass which was recrystallized as a yellow powder from 95% ethanol, m. p. 89-93°; yield 2.6 g. (41%).

The solid upon subsequent recrystallizations from 95% ethanol gave pale yellow crystals, m. p. 97-98°.

Anal.: Calcd. for $C_{22}H_{21}NO$: C, 83.77; H, 6.71; N, 4.44. Found: C, 83.40; H, 6.62; N, 4.74.

Two other runs were attempted but such extensive decomposition occurred during distillation that none of the desired product was obtained.

9-(4-Dimethylaminophenyl)anthracene (108).

A solution of 0.95 g. (0.003 mole) of 2-benzyl-4'-dimethylaminobenzophenone and 45 ml. of a 2:1 mixture of glacial acetic acid and 48% hydrobromic acid was refluxed for 6 hrs. in a 100 ml. round-bottomed flask. The solution was neutralized with 40% potassium hydroxide

and a yellow precipitate formed upon addition of the base. The solid was filtered and recrystallized from absolute ethanol as yellow needles, m. p. 254-255°; yield 0.88 g. (99%).

Anal.: Calcd. for $C_{22}H_{19}N$: C, 88.85; H, 6.44; N, 4.71. Found: C, 88.65; H, 6.33; N, 4.98.

An additional run was made using 0.5 g. (0.0015 mole) of the ketone resulting in 0.44 g. (94%) of the product.

2-(1-Naphthylmethyl)-4'-dimethylaminobenzophenone (91).

A Grignard reagent[150] was prepared from 11 g. (0.45 g. atom) of magnesium turnings activated by 0.8 ml. of ethyl bromide in 40 ml. of anhydrous ether and a mixture of 40 g. (0.2 mole) of p-bromodimethylaniline, 6.2 ml. (total of 0.09 mole) of ethyl bromide in 150 ml. of anhydrous ether which was in a 1 l. 3-necked flask equipped with a mechanical stirrer, take-off condenser and separatory funnel. To this Grignard reagent was added 15 g. (0.07 mole) of 2-(1-naphthylmethyl)benzonitrile in 50 ml. of anhydrous benzene. Following the addition of the nitrile, 200 ml. of anhydrous toluene was added and the ether removed until the boiling point of the solution reached 85° and

then the mixture was refluxed for 2 hrs. The mixture was hydrolyzed with 500 ml. of 25% sulfuric acid and this mixture refluxed for 13 hrs. The organic layer was separated from the acid layer, washed twice with water, twice with dilute sodium bicarbonate solution and once again with water, dried over anhydrous magnesium sulfate, concentrated and distilled. The product was collected as a red glassy solid at 271-280° (0.7 mm.); yield 12 g. (45%).

A portion of the red solid was recrystallized from an ethanol-benzene mixture as yellow crystals, m. p. 120.5-121°.

Anal.: Calcd. for $C_{26}H_{23}NO$: C, 85.45; H, 6.34; N, 3.83. Found: C, 85.36; H, 6.40; N, 3.80.

Two additional runs were attempted but such extensive decomposition occurred during distillation that none of the desired product was obtained.

7-(4-Dimethylaminophenyl)benz[a]anthracene (107).

A solution of 1.0 g. (0.0027 mole) of 2-(1-naphthylmethyl)-4'-dimethylaminobenzophenone and 45 ml. of a 2:1 mixture of glacial acetic acid and 48% hydrobromic acid was refluxed for one hr. in a 100 ml. round-bottomed

flask. The solution was neutralized with 20% sodium hydroxide and a yellow powder precipitated upon addition of the base. The solid was filtered and recrystallized from ethanol-benzene to give yellow crystals, m. p. 192-193°; yield 0.86 g. (92%).

A portion of the product was recrystallized from ethanol-benzene, m. p. 194.5-195°.

Anal.: Calcd. for $C_{26}H_{21}N$: C, 89.88; H, 6.09; N, 4.03. Found: C, 89.75; H, 6.15; N, 4.32.

Three additional runs were made; one resulted in none of the desired product due to decomposition (possibly too long reflux time). The other two gave yields of 90% and 91%.

2-(1-Naphthylmethyl)-2'-dimethylaminobenzophenone (92).

A Grignard reagent was prepared from 5.3 g. (0.22 g. atom) of magnesium turnings activated by a crystal of iodine and 1 ml. of ethyl bromide in 40 ml. of anhydrous ether and a mixture of 15 g. (0.075 mole) of 2-bromodimethylaniline, 2 ml. of ethyl bromide and 150 ml. of anhydrous ether. To this Grignard reagent, which was in a 500 ml. 3-necked flask equipped with a magnetic stirrer, take-off condenser and separatory funnel, was

added anhydrous toluene while ether was being removed until the boiling point of the solution reached 100°. Then 18 g. (0.075 mole) of 2-(1-naphthylmethyl)-benzonitrile in 70 ml. of anhydrous toluene was added and the mixture refluxed for 26 hrs. Excess 25% sulfuric acid was added and this mixture was refluxed for 39 hrs. The organic layer was separated, the aqueous layer made basic with 25% sodium hydroxide and extracted with benzene, and the organic layers combined, dried over anhydrous magnesium sulfate, concentrated and distilled. The product was collected as a viscous red oil at 240-255° (0.13 mm.); yield 5.8 g. (21%). Unreacted nitrile (6.0 g.) was recovered during the distillation.

A portion of the red oil was dissolved in hot 95% ethanol from which yellow needles separated. These needles were recrystallized from 95% ethanol as yellow crystals, m. p. 114-115°.

Anal.: Calcd. for $C_{26}H_{23}NO$: C, 85.45; H, 6.34; N, 3.83. Found: C, 85.45; H, 6.09; N, 3.92.

Attempted Preparation of 7-(2-Dimethylaminophenyl)-benz[a]anthracene.

A solution of 2.0 g. of 2-(1-naphthylmethyl)-2'-dimethylaminobenzophenone, 50 ml. of 48% hydrobromic acid and 100 ml. of glacial acetic acid was refluxed for 5 hrs. Extensive charring occurred during the reaction. The product was worked-up in the usual manner, although after several treatments with charcoal the solution remained deep red. Upon concentration some black oil separated and the solution was decanted. This procedure was repeated several times until no more black oil separated, only a yellow solid. An ethanolic solution of this solid fluoresced green but it exhibited a characteristic benz[a]anthracene spectrum in the ultraviolet region. Upon subsequent recrystallization from 95% ethanol a yellow-brown powder was obtained, m. p. 74-75°; yield 0.12 g.

Anal.: Calcd. for $C_{26}H_{21}N$: C, 89.88; H, 6.09; N, 4.03. Found*: C, 86.12; H, 6.47; N, 1.90. (See Discussion of Results.)

Attempted Preparation of 2-(1-Naphthylmethyl)-3'-dimethylaminobenzophenone.

Repeated attempts to prepare the Grignard reagent of 3-bromodimethylaniline in the same manner as the 2- and 4-bromodimethylanilines failed.

7-(3-Dimethylaminophenyl)benz[a]anthracene (111).

A lithium reagent was prepared from 14 g. (0.046 mole) of 2-(1-naphthylmethyl)bromobenzene and 0.60 g. (0.086 g. atom) of lithium ribbon in 100 ml. of anhydrous ether in a 250 ml. 3-necked flask equipped with a magnetic stirrer, reflux condenser and separatory funnel. To the blackish-red lithio derivative was added as fast as refluxing would allow 7.6 g. (0.046 mole) of 3-dimethylaminobenzoic acid in 100 ml. of anhydrous ether. The resulting yellow solution was stirred at room temperature for 17 hrs. and hydrolyzed with 150 ml. of water. The mixture was extracted with ether, and the ether extracts dried over anhydrous magnesium sulfate and concentrated. The resulting oil was dissolved in hot 95% ethanol and a yellow solid separated on cooling, m. p. 140-143°; yield 1.2 g. (7%). The

filtrate was re-concentrated and upon distillation, 6.9 g. of 2-(1-naphthylmethyl)bromobenzene was recovered.

The yellow solid, representing 15% yield based on unrecovered bromo compound, was recrystallized from 95% ethanol, m. p. 143-144°.

Anal.: Calcd. for $C_{26}H_{21}N$: C, 89.88; H, 6.09; N, 4.03. Found*: C, 89.65; H, 6.15; N, 4.15.

Attempted Preparation of Cyclopropyl 1-(2-Benzyl)-naphthyl Ketone.

A Grignard reagent was prepared from 40 g. (0.13 mole) of 1-bromo-2-benzylnaphthalene, 3.6 g. (0.15 g. atom) of magnesium turnings and a drop of methyl iodide in 100 ml. of anhydrous ether in a 1 l. 3-necked flask equipped with a mechanical stirrer, take-off condenser and separatory funnel. A solution of 10 g. (0.13 mole) of cyclopropyl cyanide and 350 ml. of anhydrous benzene was added dropwise to the Grignard reagent. Ether was removed until the boiling point of the solution reached 68° and the heating continued for 8 hrs. The mixture was hydrolyzed with 20% ammonium chloride (0.3 mole) solution. The resulting mixture was extracted with ether, dried over anhydrous magnesium sulfate, concentrated and distilled. The product was collected

as a very viscous yellow oil at 223-226° (2 mm.); yield 24 g. This oil turned red in 95% ethanol or carbon tetrachloride.

It was suspected (see Discussion of Results, Section B.4) that this product was 2-benzyl-1-(2-Δ'-pyrrolinyl)naphthalene (98) with the above yield representing 62% of the theoretical. A portion of the oil was redistilled with the product distilling sharply at 166° (0.05 mm.) with subsequent solidification, m. p. 84-86°.

Anal.: Calcd. for $C_{21}H_{19}N$: C, 88.38; H, 6.71; N, 4.91. Found: C, 88.42; H, 6.50; N, 4.81.

Two additional runs were made using different quantities of starting materials. One, using 15 g. (0.05 mole) of the bromo compound and 2.3 g. (0.035 mole) of the nitrile, resulted in 5.6 g. (56%) of the product. The other, using 30 g. (0.1 mole) of the bromo compound and 5.4 g. (0.08 mole) of the nitrile, resulted in 19.5 g. (88%) of the desired product.

A half-gram sample of 2-benzyl-1-(2-Δ'-pyrrolinyl)-naphthalene was mixed with 0.25 g. of selenium powder[160] and heated at 160-175° under a slow stream of nitrogen for 2 hrs. The mixture was extracted with boiling

toluene, filtered through glass wool and cooled. The clear solution was concentrated and turned red on standing in the air. The product, a reddish solid, was heated with fluorescein chloride (3',6'-dichlorofluoran) and anhydrous zinc chloride and the melt dissolved in 10% alcoholic hydrochloric acid, resulting in a yellow-brown dye - a positive test for pyrroles.[161]

Attempted Preparation of Cyclopropyl 2-(2-Naphthylmethyl)phenyl Ketone (102).

A Grignard reagent was prepared from 30 g. (0.10 mole) of 2-(2-naphthylmethyl)bromobenzene, 2.4 g. (0.10 g. atom) of magnesium turnings and a drop of methyl iodide in 125 ml. of anhydrous ether in a 1 l. 3-necked flask equipped with a mechanical stirrer, reflux condenser and a separatory funnel. A solution of 6.7 g. (0.10 mole) of cyclopropyl cyanide and 100 ml. of anhydrous ether was added dropwise to the Grignard reagent and the mixture heated under reflux for 2 hrs. The mixture was hydrolyzed with 150 ml. (excess) of 20% ammonium chloride and extracted with ether. The ethereal solution was dried over anhydrous magnesium sulfate, concentrated and distilled. The major

fraction was collected as a yellow viscous oil at 209-210° (0.2 mm.); yield 13 g. This oil was dissolved in hot 95% ethanol and upon cooling, tiny pale yellow needles separated (0.28 g.). The solution was concentrated and redistilled and a center-cut taken at 208.5-209° (0.15 mm.).

The pale yellow needles were shown to be 5-cyclopropylnaphthacene (103) with the above yield representing 1% yield. (See Discussion of Results, Section B.5.) They were recrystallized from 95% ethanol, m. p. 133° (sublimation).

Anal.: Calcd. for $C_{21}H_{16}$: C, 93.99; H, 6.01. Found*: C, 94.05; H, 6.06.

The oil was shown to be 2-(2-Δ^1-pyrrolinyl)-phenyl-2-naphthylmethane (99) with the 13 g. representing 45% of the theoretical yield.

Anal.: Calcd. for $C_{21}H_{19}N$: C, 88.38; H, 6.71; N, 4.91. Found*: C, 88.37; H, 6.74; N, 4.56.

Action of Cyclopropyl Cyanide on 2-(1-Naphthylmethyl)-phenylmagnesium Bromide.

A. Aqueous Ammonium Chloride Hydrolysis.

A Grignard reagent was prepared from 2.7 g. (0.11 g. atom) of magnesium turnings and 30 g. (0.10 mole) of 2-(1-naphthylmethyl)bromobenzene dissolved in 100 ml. of anhydrous ether in a 1 l. 3-necked flask equipped with a magnetic stirrer, take-off condenser and separatory funnel. To this Grignard reagent was added 6.7 g. (0.10 mole) of cyclopropyl cyanide in 100 ml. of anhydrous benzene. Following the addition, 100 ml. of additional benzene was added and ether removed until the boiling point of the solution reached 65°, at which temperature the mixture was heated for 4.5 hours. The mixture was hydrolyzed with 140 ml. (excess) of 20% ammonium chloride solution and extracted with benzene. The benzene extracts were dried over anhydrous magnesium sulfate, concentrated and distilled. The major fraction was collected as a viscous yellow oil at 207-212° (1.5 mm.); yield 16 g. This product crystallized as tiny white needles from 95% ethanol, m. p. 158.5-159.5°, and was characterized (see Section C.4, Discussion of Results) as 7-cyclopropylbenz[a]anthracene (114) with the above yield representing 54% of the theoretical.

Anal.: Calcd. for $C_{21}H_{16}$: C, 93.99; H, 6.01. Found: C, 94.24; H, 5.72.

Two additional runs were made using the same quantities as above (50% yield) and one-half quantities (55%).

B. Excess Water Hydrolysis.

The experiment in part A was repeated except that the hydrolysis of the Grignard reagent was effected by addition of 100 ml. of water. The mixture was worked-up in the same manner, resulting in identical product; yield 11 g. (39%).

C. Equimolar Water Hydrolysis.

The experiment in part A was repeated in one-third quantities except the hydrolysis of the Grignard reagent was effected by addition of 0.72 g. (equimolar) of water. The organic layer was decanted from the resulting solid, and the solid extracted with boiling anhydrous benzene. The combined benzene extracts were treated with anhydrous hydrogen chloride. The resulting precipitate was filtered and dried by aspiration; yield 6 g. (crude yield representing 55% expected ketimine hydrochloride salt).

7-(3-Acetoxypropyl)benz[a]anthracene (116).

To 0.85 g. of the above ketimine hydrochloride (cyclopropyl 2-[1-naphthylmethyl]phenyl ketimine hydrochloride) (see Section C.4, Discussion of Results) in a 100 ml. round-bottomed flask was added a mixture of 50 ml. of acetic anhydride saturated with anhydrous hydrogen chloride. The mixture was refluxed for 2 hrs. The solution was poured into 300 ml. of water and extracted with ether. The ether extracts were dried over anhydrous magnesium sulfate and concentrated; a gray powder precipitated, which was recrystallized from 95% ethanol, m. p. 184.5-186°; yield 0.35 g. (41%).

Anal.: Calcd. for $C_{23}H_{20}O_2$: C, 84.12; H, 6.14. Found*: C, 84.40; H, 6.59.

Cyclopropyl 2-(2-Naphthylmethyl)phenyl Ketone (102).

A Grignard reagent was prepared from 15 g. (0.05 mole) of 2-(2-naphthylmethyl)bromobenzene, 1.2 g. (0.05 g. atom) of magnesium turnings, a crystal of iodine and a drop of methyl iodide in 125 ml. of anhydrous ether in a 500 ml. 3-necked flask equipped with a magnetic stirrer, reflux condenser and a separatory funnel. The ethereal solution of the Grignard reagent was added slowly to a solution of 3 g. (0.03 mole) of

cyclopropanecarboxylic acid chloride and 50 ml. of anhydrous ether. The mixture was refluxed for 5 hrs. following the addition, poured into water and worked-up in the usual manner. The product was collected as a clear viscous oil at 206-209° (0.05 mm.); yield 5 g. (56%).

The product was redistilled and a center-cut taken at 207° (0.05 mm.) for elemental analysis.

Anal.: Calcd. for $C_{21}H_{18}O$: C, 88.08; H, 6.33. Found*: C, 88.14; H, 6.60

An additional run was made using 15 g. (0.05 mole) of the bromo compound and 4 g. (0.05 mole) of the nitrile. The product obtained weighed 6 g. (52%).

Attempted Cyclization of Cyclopropyl 2-(2-Naphthylmethyl)-phenyl Ketone.

A. Via Aqueous Ammonium Chloride.

A solution of 0.5 g. of cyclopropyl 2-(2-naphthylmethyl)phenyl ketone dissolved in 50 ml. of 95% ethanol and 25 ml. of 20% ammonium chloride was refluxed for 12 hrs. The mixture was extracted with ether and the ether extract was concentrated and the resulting oil was shown by its infrared and ultraviolet spectra to be starting material.

B. Via Phenyl Acid Phosphate.[d]

A mixture of 0.9 g. of the above ketone and 6.0 g. of phenyl acid phosphate was heated for 0.5 hr. at 100° (pyrometer reading). The dark mixture was allowed to stand at room temperature overnight and then hydrolyzed with 150 ml. of water. The resulting mixture was extracted with ether, the ether extracts concentrated and the resulting oil dissolved in 95% ethanol. Although the ultraviolet spectrum of this solution indicated the presence of a benz[a]anthracene system, all attempts of purification of the product failed.

C. Via Polyphosphoric Acid.

A mixture of 1.8 g. of the same ketone and 8.0 g. of polyphosphoric acid was heated for 2 hrs. at 100-120° (pyrometer reading). The excess polyphosphoric acid was hydrolyzed with 150 ml. of water followed by an additional hour of heating. The reaction mixture was extracted with ether and worked-up as part B. Although the ultraviolet spectrum of the oily product indicated the presence of

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d Phenyl acid phosphate was obtained from Virginia-Carolina Chemical Corporation. This acid is a mixture of phenyl dihydrogen phosphate and diphenyl hydrogen phosphate.

the benz[a]anthracene system, no pure isolable product was obtained.

D. Via Alumina.

A mixture of 1.0 g. of the same ketone and 40 g. of natural alumina was heated under reduced pressure (2 mm.) at 175-200° for 4 hrs. The alumina was extracted with petroleum ether (30-60°) overnight in a Soxhlet extractor, followed by 8 hrs. extraction with benzene. No organic material was found in either extract.

E. Via Hydriodic Acid-Acetic Acid.

A mixture of 1.5 g. of the same ketone, 30 ml. of 57% hydriodic acid and 10 ml. of glacial acetic acid was gently refluxed for 12 hrs. To the cooled mixture 100 ml. of water was added and the solution extracted with ether. The ether extract was washed with 10% sodium thiosulfate, then water, and was then concentrated. The oil was dissolved in hot 95% ethanol from which two solid fractions were obtained. The first fraction was a white powder, m. p. 108.5-109.5°; yield 0.4 g. The second fraction was a yellow solid, m. p. 139-142°; yield 0.3 g. Neither fraction could be identified.

Hydrogen Fluoride Action on Benzene.

In a 1/2 pint polyethylene bottle equipped with a magnetic stirrer was placed 20 ml. of anhydrous benzene. Upon usual addition of hydrogen fluoride an exothermic reaction occurred evidenced by vigorous refluxing of the benzene.

5-Cyclopropylnaphthacene (103).

In a 1/2 pint polyethylene bottle equipped with a magnetic stirrer was placed 0.5 g. of cyclopropyl 2-(2-naphthylmethyl)phenyl ketone dissolved in 20 ml. of anhydrous benzene. The vigor of the exothermic reaction with benzene alone was moderated in this case upon addition of hydrogen fluoride. Approximately 5 ml. of hydrogen fluoride was added resulting in immediate precipitate formation. The hydrogen fluoride was allowed to evaporate and the contents of the flask were dissolved in boiling ethanol-benzene and charcoaled. An orange solid, yield 0.5 g., was isolated, m. p. 132° (sublimation). Upon recrystallization from 95% ethanol, yellow crystals separated, m. p. 133° (sublimation); yield 0.46 g. (98%).

A mixed m. p. with previously obtained 5-cyclopropylnaphthacene showed no melting point depression.

Cyclopropyl 2-(1-Naphthylmethyl)phenyl Ketone (105).

A Grignard reagent was prepared from 15 g. (0.05 mole) of 2-(1-naphthylmethyl)bromobenzene, 1.2 g. (0.05 g. atom) of magnesium turnings and a crystal of iodine in 125 ml. of anhydrous ether in a 500 ml. 3-necked flask equipped with a magnetic stirrer, reflux condenser and a separatory funnel. The ethereal solution of the Grignard reagent was added slowly to a solution of 3 g. (0.03 mole) of cyclopropanecarboxylic acid chloride and 50 ml. of anhydrous ether. The mixture was refluxed for 9 hrs. following the addition, poured into water, and extracted with benzene. The organic extract was dried over anhydrous magnesium sulfate, filtered, concentrated and distilled. The product was collected as a viscous clear oil at 192-195° (0.1 mm.); yield 5 g. (59%).

The product was redistilled and a center-cut taken at 195.5° (0.15 mm.) for elemental analysis.

Anal.: Calcd. for $C_{21}H_{18}O$: C, 88.08; H, 6.33. Found*: C, 87.70; H, 6.39.

An additional run was made using 20 g. (0.067 mole) of bromo compound. The product weighed 6 g. (30%).

Attempted Cyclization of Cyclopropyl 2-(1-Naphthylmethyl)phenyl Ketone (105).

A. Via Aqueous Ammonium Chloride.

A 0.5 g. portion of cyclopropyl 2-(1-naphthylmethyl)-phenyl ketone was treated in the same manner as the 2-(2-naphthylmethyl)phenyl isomer. Following a similar work-up only starting material was obtained.

B. Via Phenyl Acid Phosphate.

A mixture of 0.8 g. of the same ketone and 6.0 g. of phenyl acid phosphate was treated in the same manner as the 2-(2-naphthylmethyl)phenyl isomer. Again the crude product gave a normal benz[a]anthracene spectrum in the ultraviolet region but no isolable pure product was obtained.

C. Via Hydriodic Acid.

A solution of 0.5 g. of the same ketone, 25 ml. of 57% hydriodic acid and 15 ml. of 95% ethanol was heated under reflux for 12 hrs. The mixture was diluted with 100 ml. of water and extracted with ether. The ether extract was washed with 10% sodium thiosulfate and then

with water, and concentrated. The resulting oil was dissolved in hot 95% ethanol. Yellow-green crystals separated, m. p. 123-125° (decomposition); yield 0.3 g. It was suspected the product was 7-(3-iodopropyl)-benz[a]anthracene.

Anal.: Calcd. for $C_{21}H_{17}I$: C, 63.65; H, 4.32; I, 32.03. Found*: C, 83.98; H, 6.59; I, 8.58. (See Discussion of Results, Section C.4.)

From the mother-liquor was obtained 0.05 g. of white crystals, m. p. 158-159°. This product gave an ultraviolet spectrum identical to that of 7-cyclopropylbenz[a]anthracene.

D. Via Hydrobromic Acid - Acetic Acid.

A mixture of 0.5 g. of the same ketone, 20 ml. of 48% hydrobromic acid and 40 ml. of glacial acetic acid was refluxed 30 min. A black tar resulted and after the usual work-up no isolable product was obtained although an alcoholic solution of the reaction product gave a normal benz[a]anthracene ultraviolet spectrum.

7-Cyclopropylbenz[a]anthracene.

A. Via Nitrile and Grignard Reagent.

This method resulting in 54% yield has been previously recorded.

B. Via Phosphorus Pentoxide.

A mixture of 0.4 g. of cyclopropyl 2-(1-naphthylmethyl)phenyl ketone, 2.0 g. of phosphorus pentoxide and 50 ml. of anhydrous benzene was refluxed 45 min. The excess phosphorus pentoxide was hydrolyzed with 100 ml. of water. The reaction mixture was extracted with boiling benzene. From the cooled extract precipitated white crystals, m. p. 158.5-159.5°; yield 0.18 g. (48%). A mixed melting point with the product from part A showed no depression.

C. Via Potassium Hydroxide - Quinoline.

A mixture of 0.4 g. of the same ketone, 2.5 g. of powdered potassium hydroxide pellets and 25 ml. of quinoline was heated at 130° for 45 min. Water (2 l.) was added and the solution extracted with benzene and then ether. The combined benzene - ether extracts were concentrated and the quinoline distilled from the mixture. The remaining oil was dissolved in hot 95% ethanol. From the cooled solution precipitated a brown

solid which on recrystallization from 95% ethanol yielded white crystals, m. p. 158-159.5°; yield 0.07 g. (19%).

D. Via Hydrogen Fluoride.

To 0.6 g. of the same ketone was added with stirring 50 ml. of liquid hydrogen fluoride. Extensive decomposition occurred during the addition, but following the usual work-up procedure a white powder separated from the alcoholic extract, m. p. 158-160°; yield 0.14 g. (26%).

To 0.5 g. of the same ketone dissolved in 20 ml. of anhydrous benzene, hydrogen fluoride was added dropwise over a 30 second period. Immediate precipitation occurred. Following the usual work-up, the desired product was obtained, m. p. 157-159.5°; yield 0.2 g. (45%).

Reactivity of 7-cyclopropylbenz[a]anthracene

A. Platinum Oxide.

A mixture of 1.0 g. of 7-cyclopropylbenz[a]anthracene dissolved in 150 ml. of ethyl acetate and 0.25 g. of platinum oxide (83.44% platinum oxide obtained from Engelhard Industries, Inc., Newark, N. J.) was placed in a 500 ml. hydrogenation reaction jar. The hydrogenation apparatus was evacuated by a water

aspirator, flushed twice with hydrogen and reevacuated. Then hydrogen was added (40 p.s.i.) and the reaction jar shaken for 3 hrs. The contents of the jar were filtered through a medium sintered glass funnel, the solvent was removed and the resulting oil was crystallized from 95% ethanol. The starting material was recovered unchanged, m. p. 157-158°. A mixed melting point of the reaction product with the starting material resulted in no depression; a mixed melting point of the product and benz[a]anthracene, 123-129°.

B. Raney Nickel.

A mixture of 1.0 g. of 7-cyclopropylbenz[a]-anthracene dissolved in 200 ml. of 95% ethanol and 1/2 teaspoon of Raney nickel (activation approximately W-4) was placed in a 500 ml. hydrogenation reaction jar. The hydrogenation attempt was carried out as in part A, the time of shaking being 4 hrs. The contents of the jar were filtered through a medium sintered glass funnel. During concentration of the filtrate, all the unreacted starting material crystallized, m. p. 157.5-159°; a mixed melting point with starting material caused no depression.

C. Acetic Acid.

A solution of 0.2 g. of 7-cyclopropylbenz[a]anthracene and 40 ml. of glacial acetic acid was refluxed for 2 hrs.

There was no visible reaction and a milliliter aliquot was removed and used to obtain an ultraviolet spectrum which was identical with that of the starting material. To the reaction mixture was then added 1.5 ml. of concentrated sulfuric acid and the heating continued for an additional 1.5 hrs. The mixture was poured into 300 ml. of water and a solid precipitated on cooling. The white solid's melting point and ultraviolet spectrum were identical with those of the starting material.

D. Hydriodic Acid.

A mixture of 0.5 g. of cyclopropylbenz[a]anthracene and 30 ml. of 57% hydriodic acid was refluxed heterogeneously for 5 hrs. The reaction was cooled and worked-up in the usual manner. The starting material was quantitatively recovered.

To assure homogeneity the above reaction was repeated using 10 ml. of anhydrous benzene. The solution was refluxed 9 hrs. Again quantitative recovery of starting material was effected, m. p. 158-159.5°. A mixed melting point with benz[a]anthracene was depressed, m. p. 130-135°.

E. Hydrobromic Acid - Acetic Acid.

A solution of 0.2 g. of 7-cyclopropylbenz[a]-anthracene, 20 ml. of 48% hydrobromic acid and 40 ml.

of glacial acetic acid was refluxed for 4 hrs. Upon addition of water a white solid precipitated; yield 0.16 g. This product was shown by melting point and ultraviolet spectrum to be unreacted starting material.

F. 2,4,7-Trinitrofluorenone.

To 0.1 g. of 7-cyclopropylbenz[a]anthracene dissolved in hot 95% ethanol and a small amount of benzene was added an equimolar amount of 2,4,7-trinitrofluorenone dissolved in hot 95% ethanol. No visible reaction occurred, and after the solvent was allowed to evaporate into the air over a 4 day period two forms of crystals separated. A crystal of one of these forms was separated and by means of melting point was shown to be starting material.

Cyclopropyl 2-Benzylphenyl Ketone (106).

A Grignard reagent was prepared from 10 g. (0.04 mole) of 2-bromodiphenylmethane, 0.97 g. (0.04 g. atom) of magnesium turnings and a crystal of iodine in 85 ml. of anhydrous ether in a 500 ml. 3-necked flask equipped with a magnetic stirrer, reflux condenser and a separatory funnel. The ethereal solution of the Grignard reagent was added slowly to a solution of

3.7 g. (0.035 mole) of cyclopropanecarboxylic acid chloride and 80 ml. of anhydrous ether. The mixture was refluxed for 4 hrs. following the addition, poured into water and worked-up in the usual manner. The product was collected as a pale yellow liquid at 165-170° (0.5 mm.); yield 4 g. (51%).

The product was redistilled and a center-cut taken at 163° (0.5 mm.) for chemical analysis.

Anal.: Calcd. for $C_{17}H_{16}O$: C, 86.40; H, 6.83. Found*: C, 86.34; H, 6.55.

An additional run was made using the same amount of reagents. The product weighed 2.6 g. (28%).

9-Cyclopropylanthracene (127).

A. Via Hydrogen Fluoride.

To 0.6 g. of cyclopropyl 2-benzylphenyl ketone dissolved in 20 ml. of anhydrous benzene was added approximately 2 ml. of liquid hydrogen fluoride. Following the usual work-up, a pale yellow oil was obtained which, although its ultraviolet spectrum indicated that an anthracene system was present, was shown to be mainly ketone as indicated by comparison

of the infrared spectra of the starting material and product.

B. Via Phosphorus Pentoxide.

A mixture of 0.5 g. of the same ketone, 25 ml. of anhydrous toluene and 3 g. of phosphorus pentoxide was refluxed for 2.5 hrs. The mixture was extracted with benzene. The aqueous layer was made basic with 25% sodium hydroxide and extracted with boiling toluene. The organic extracts were combined and concentrated. A gummy yellow solid was obtained and following unsuccessful attempts at crystallization by freezing and from 95% ethanol, benzene, petroleum ether (30-60°), carbon tetrachloride, ethanol-benzene, n-hexane, and methanol, the yellow gum was crystallized from methanol-ether, m. p. 57-58°; yield 0.1 g. (21%).

The product was recrystallized from methanol-ether as white crystals, m. p. 58.5-59°.

Anal.: Calcd. for $C_{17}H_{14}$: C, 93.54; H, 6.46. Found*: C, 93.39; H, 6.34.

SUMMARY

SUMMARY

The Grignard reagent cross-condensation reaction was extended in scope. This method was used to synthesize 2-bromodiphenylmethane (63), 2-(1-naphthylmethyl)chlorobenzene (80) and 2-(1-naphthylmethyl)bromobenzene (65).

The base-catalyzed cyclization reaction between an appropriate carboxylic acid and an appropriate lithium derivative was used to prepare 7-(3-dimethylaminophenyl)benz[a]anthracene (111). This cyclized product was obtained by use of the above method since the normal acid-catalyzed cyclization of the corresponding ketone was not practical. The ketone could not be prepared by usual procedures since the Grignard reagent of 3-bromodimethylaniline will not form.

7-(2-Dimethylaminophenyl)benz[a]anthracene could not be prepared from the corresponding ketone through use of the usual methods of cyclization. The reason for this resistance to normal cyclization was discussed in detail.

Anomalous products were isolated from the reaction between cyclopropyl cyanide and certain Grignard reagents. These products were shown to be isomeric

with the expected ketimines and were identified as the corresponding pyrroline compounds. The reason for this rearrangement and proof of structure were discussed in detail.

A minute amount of 5-cyclopropylnaphthacene (103) was isolated along with one of the pyrrolines. When cyclopropyl cyanide was added to 2-(1-naphthylmethyl)-phenylmagnesium bromide, the cyclized product, 7-cyclopropylbenz[a]anthracene (114), was obtained in high yield to the exclusion of any pyrroline. Electronic effects, coupled with steric hindrance, were discussed as possible explanations for these results.

Possible reasons were discussed for the observed pronounced stability of a cyclopropyl ring attached to a polynuclear system in contrast to the reactivity of the corresponding ketone.

A modification of the usual hydrogen fluoride cyclization procedure resulted in near quantitative yield of 5-cyclopropylnaphthacene from cyclopropyl 2-(2-naphthylmethyl)phenyl ketone. An explanation of this new cyclization route and of the potency of the hydrogen fluoride modification was discussed.

12-Cyclopropylbenz[a]anthracene could not be prepared by any of the usual procedures. Evidence

for the sterically controlled impossibility of formation of this compound was presented. The ease of formation of the corresponding naphthacene derivative, a heretofore unobserved ring closure in This Laboratory, supports the supposition that ring closure to give a 12-substituted benz[a]anthracene will not occur in the case of the cyclopropyl group.

During the course of this investigation sixteen new compounds were prepared. One derivative of an intermediate was obtained: 2-benzyl-1-cyanonaphthalene (77). Six ketone precursors of the final cyclized compounds were prepared. They are: 2-benzyl-4'-dimethylaminobenzophenone (90), 2-(1-naphthylmethyl)-4'-dimethylaminobenzophenone (91), 2-(1-naphthylmethyl)-2'-dimethylaminobenzophenone (92), cyclopropyl 2-benzylphenyl ketone (106), cyclopropyl 2-(1-naphthylmethyl)-phenyl ketone (105), cyclopropyl 2-(2-naphthylmethyl)-phenyl ketone (102).

Two pyrrolines were obtained as rearrangement products. They are: 2-benzyl-1-(2-Δ^1-pyrrolinyl)-naphthalene (98) and 2-(2-Δ^1-pyrrolinyl)phenyl-2-naphthylmethane (99).

The seven new cyclized compounds that were prepared are: 9-(4-dimethylaminophenyl)anthracene (108),

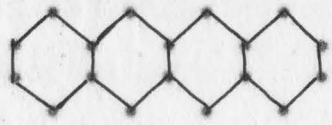
7-(4-dimethylaminophenyl)benz[a]anthracene (107)*, 7-(3-dimethylaminophenyl)benz[a]anthracene (111)*, 7-cyclopropylbenz[a]anthracene (114)*, 5-cyclopropylnaphthacene (103)*, 9-cyclopropylanthracene (127), 7-(3-acetoxypropyl)benz[a]anthracene (116). The four compounds marked with an asterisk were prepared in quantities sufficient for carcinolytic screening.

Infrared and ultraviolet spectral interpretations were given for the new compounds.

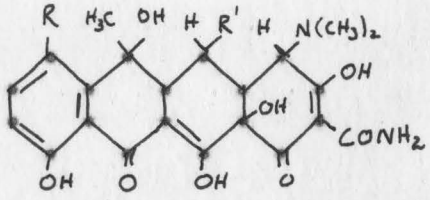
SUGGESTIONS FOR FUTURE WORK

SUGGESTIONS FOR FUTURE WORK

The facile formation of the naphthacene system from the cyclization of sterically hindered ketones by the newly described catalyst, hydrogen fluoride-benzene, warrants further study. The structural relationship between the naphthacene system and the extremely physiologically important tetracyclines cannot be ignored.



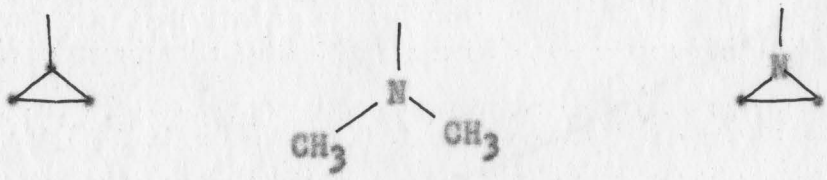
Naphthacene



Tetracyline

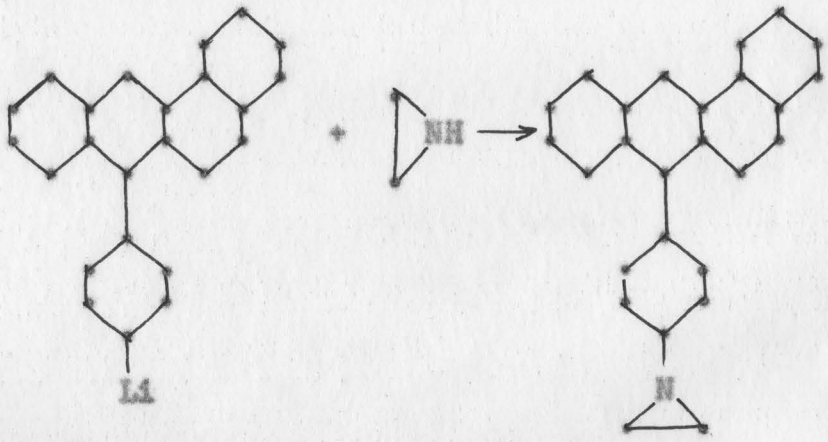
Experimentation to determine the course of action of similar ketones to produce other alicyclic substituted polynuclear compounds could further elucidate the driving force behind the cyclization. Synthesis of the cyclobutyl, cyclopentyl and cyclohexyl benz[a]anthracenes and naphthacenes would indicate the relative importance of steric factors and electronic effects.

Another synthetic problem combining the structural properties of the cyclopropyl and dimethylamino derivatives would be the preparation of aziridine derivatives. Aziridines are extremely important not



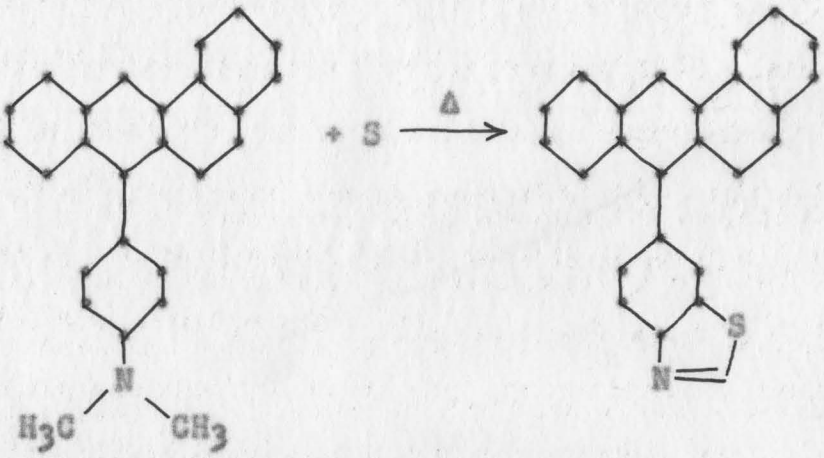
only in cancer chemotherapy but also in other physiologically allied fields.

A possible scheme for the preparation of aziridine derivatives of the benz[a]anthracene and naphthacene systems can be illustrated by the following example.

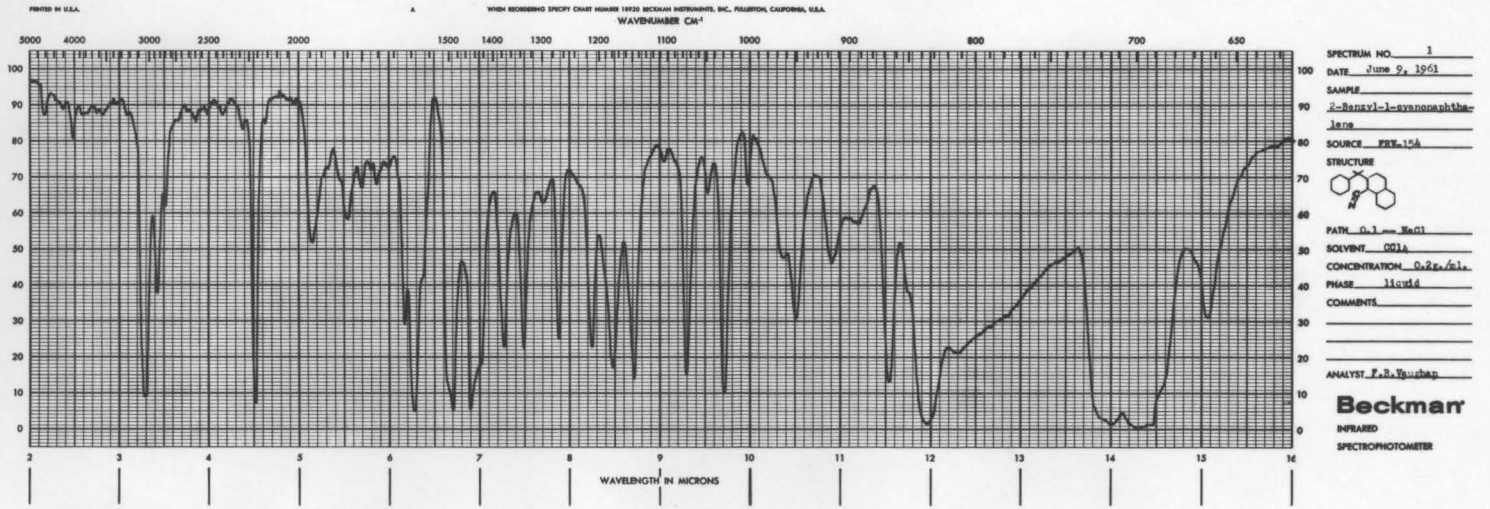


The dimethylaminophenylbenz[a]anthracene could be treated with elemental sulfur to produce the corresponding benzothiazole derivatives.[208] The

thiazole system is found in several physiologically important compounds, such as penicillin and thiamine.



APPENDIX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DATE June 9, 1961
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SOURCE FRK-154
STRUCTURE
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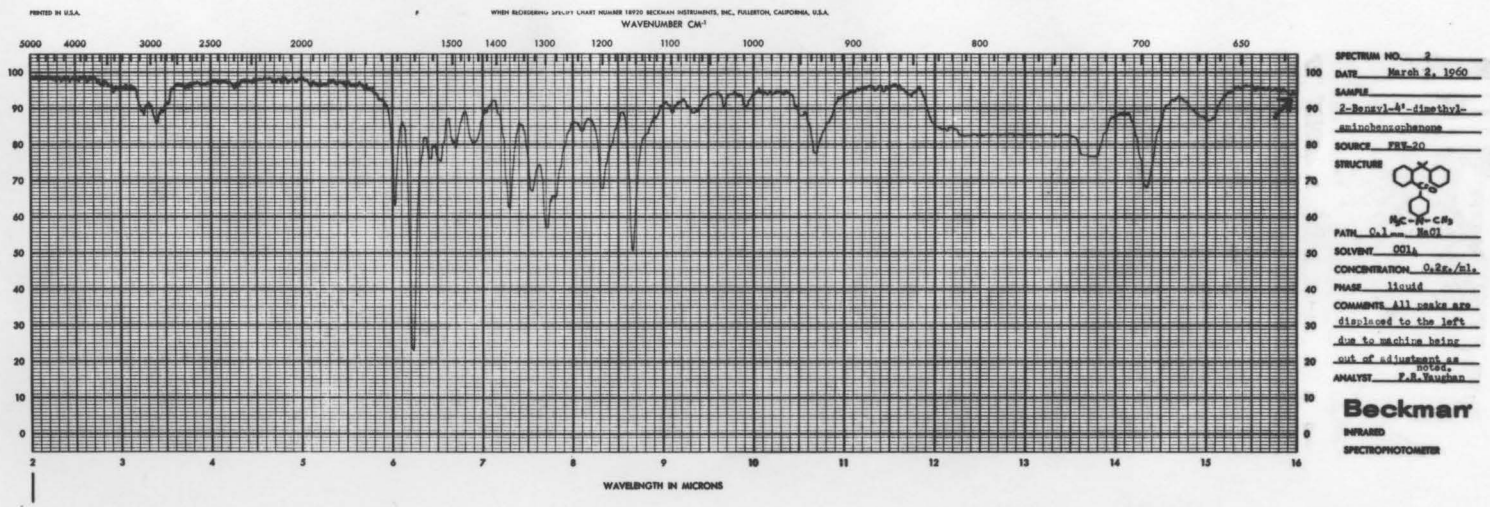
SOLVENT CCl4
CONCENTRATION 0.2g./ml.
PHASE liquid
COMMENTS
ANALYST F.R.Vaughan
Beckman
INFRARED
SPECTROPHOTOMETER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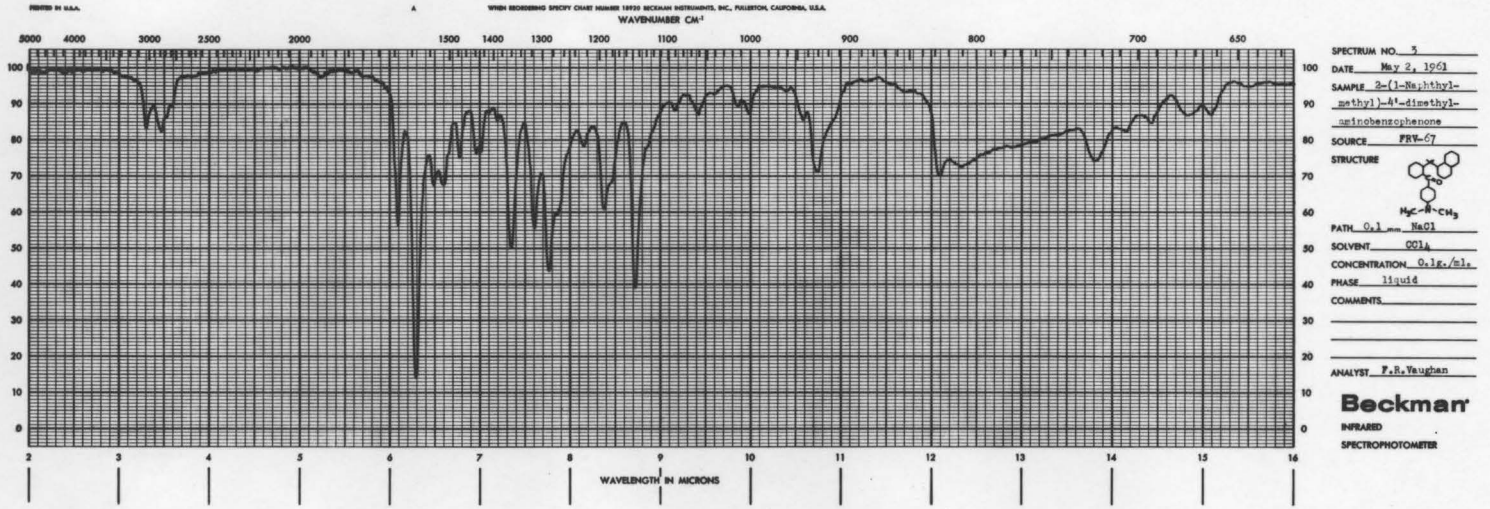
PATH 0.1 mm NaCl
SOLVENT CCl4
CONCENTRATION 0.2g./ml.
PHASE liquid
COMMENTS All peaks are displaced to the left due to machine being out of adjustment as noted.
ANALYST F.R.Vaughan
Beckman
INFRARED
SPECTROPHOTOMETER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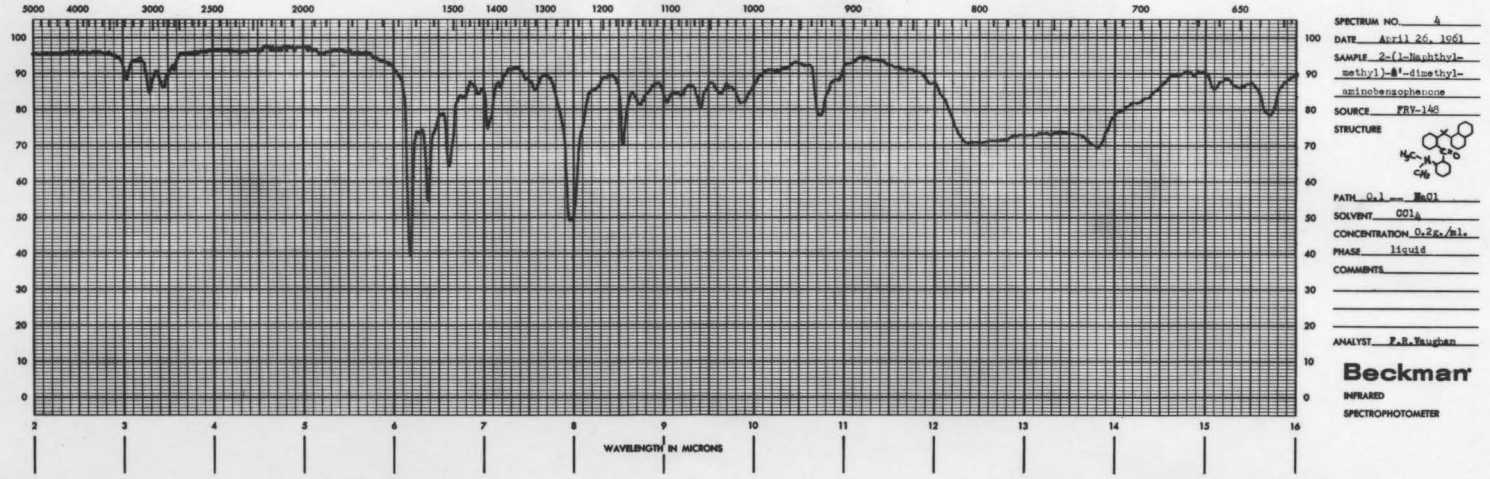
2 3 4 5 6 7 8 9 10 11 12 13 14 15 16
WAVELENGTH IN MICRONS
SPECTRUM NO. 3
DATE May 2, 1961
SAMPLE 2-(1-Naphthyl-methyl)-4'-dimethyl-aminobenzophenone
SOURCE FRV-67
STRUCTURE
PATH 0.1 mm NaCl
SOLVENT CCl4
CONCENTRATION 0.1g./ml.
PHASE liquid
COMMENTS
ANALYST F.R.Vaughan
Beckman
INFRARED
SPECTROPHOTOMETER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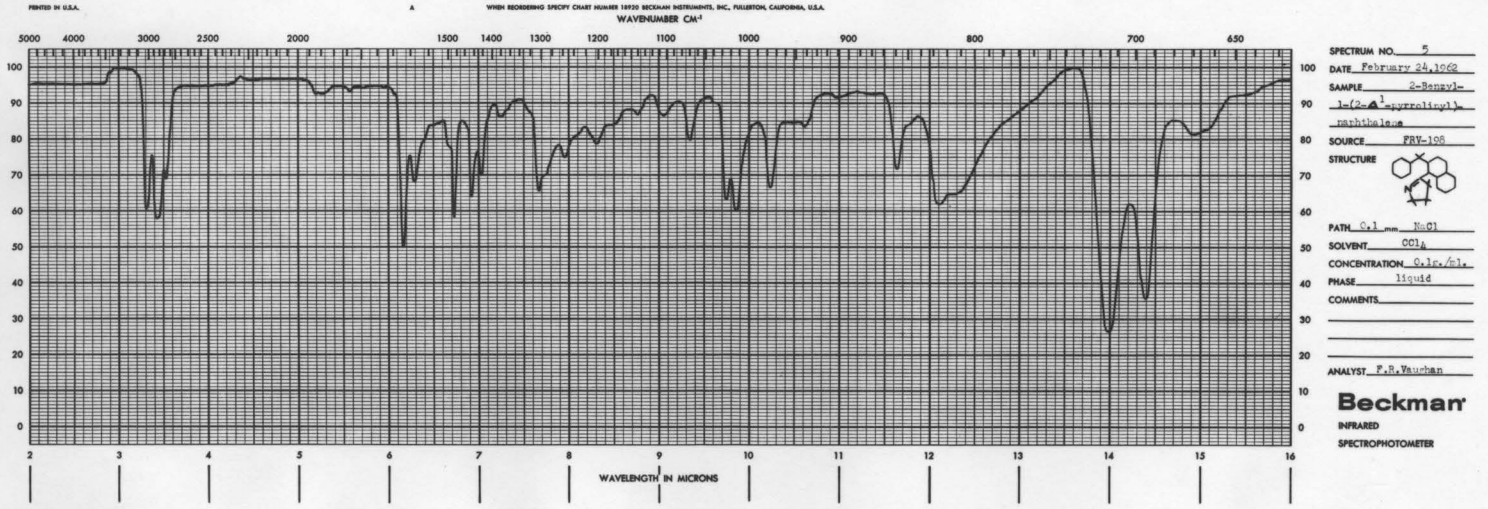
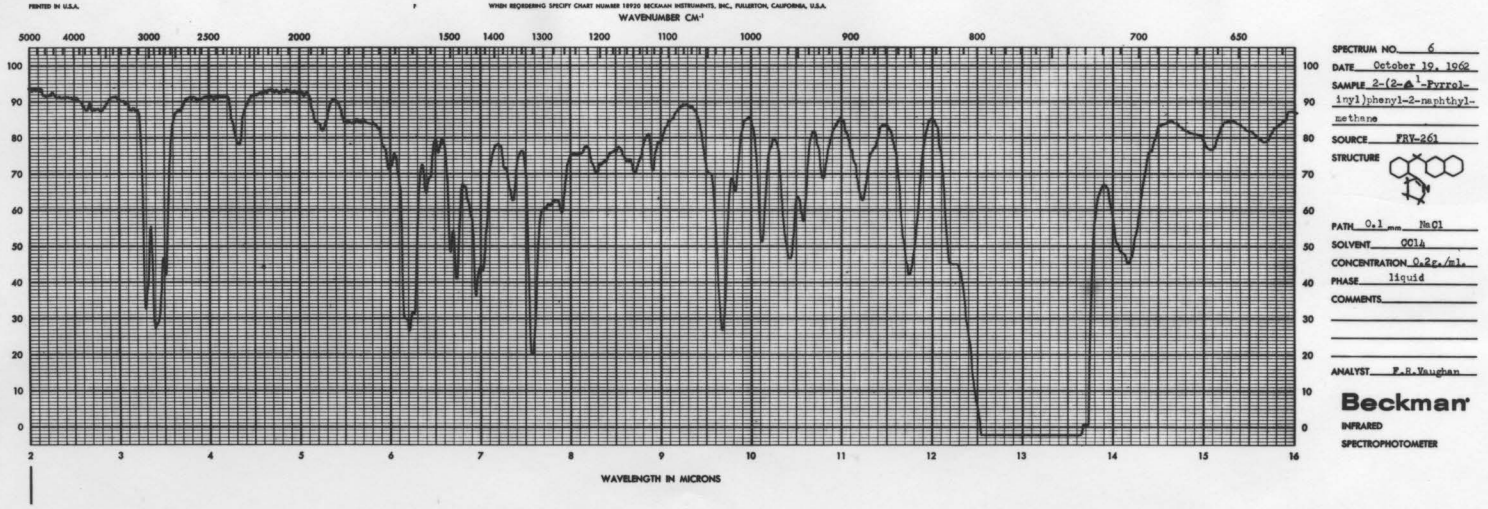
100 90 80 70 60 50 40 30 20 10 0
2 3 4 5 6 7 8 9 10 11 12 13 14 15 16
WAVELENGTH IN MICRONS
SPECTRUM NO. 4
DATE April 26, 1961
SAMPLE 2-(1-Naphthyl-methyl)-4'-dimethyl-aminobenzophenone
SOURCE FRV-148
STRUCTURE
PATH 0.1 mm NaCl
SOLVENT CCl4
CONCENTRATION 0.2g./ml.
PHASE liquid
COMMENTS
ANALYST F.R.Vaughan
Beckman
INFRARED
SPECTROPHOTOMETER


PRINTED IN U.S.A.
WHEN REORDERING SPECIFY CHART NUMBER 10920 BECKMAN INSTRUMENTS, INC., FULLERTON, CALIFORNIA, U.S.A.
WAVENUMBER CM-1
5000 4000 3000 2500 2000 1500 1400 1300 1200 1100 1000 900 800 700 650
100 90 80 70 60 50 40 30 20 10 0
2 3 4 5 6 7 8 9 10 11 12 13 14 15 16
WAVELENGTH IN MICRONS
SPECTRUM NO. 5
DATE February 24,1962
SAMPLE 2-Benzyl-1-(2-Δ1-pyrrolinyl)-naphthalene
SOURCE FRV-106
STRUCTURE
PATH 0.1 mm NaCl
SOLVENT CCl4
CONCENTRATION 0.1g./ml.
PHASE liquid
COMMENTS
ANALYST F.R.Vaughan
Beckman
INFRARED
SPECTROPHOTOMETER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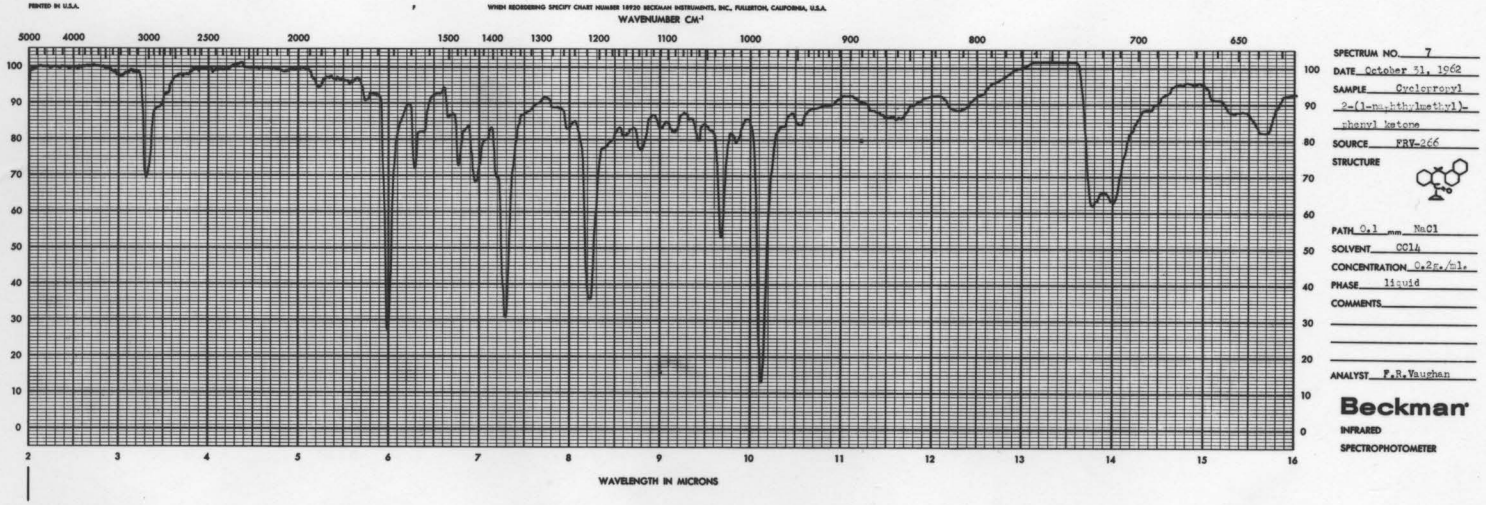
WAVENUMBER CM-1
5000 4000 3000 2500 2000 1500 1400 1300 1200 1100 1000 900 800 700 650
100 90 80 70 60 50 40 30 20 10 0
2 3 4 5 6 7 8 9 10 11 12 13 14 15 16
WAVELENGTH IN MICRONS
SPECTRUM NO. 6
DATE October 19, 1962
SAMPLE 2-(2-Δ1-Pyrrolinyl)phenyl-2-naphthylmethane
SOURCE FRV-261
STRUCTURE
PATH 0.1 mm NaCl
SOLVENT CCl4
CONCENTRATION 0.2g./ml.
PHASE liquid
COMMENTS
ANALYST F.R.Vaughan
Beckman
INFRARED
SPECTROPHOTOMETER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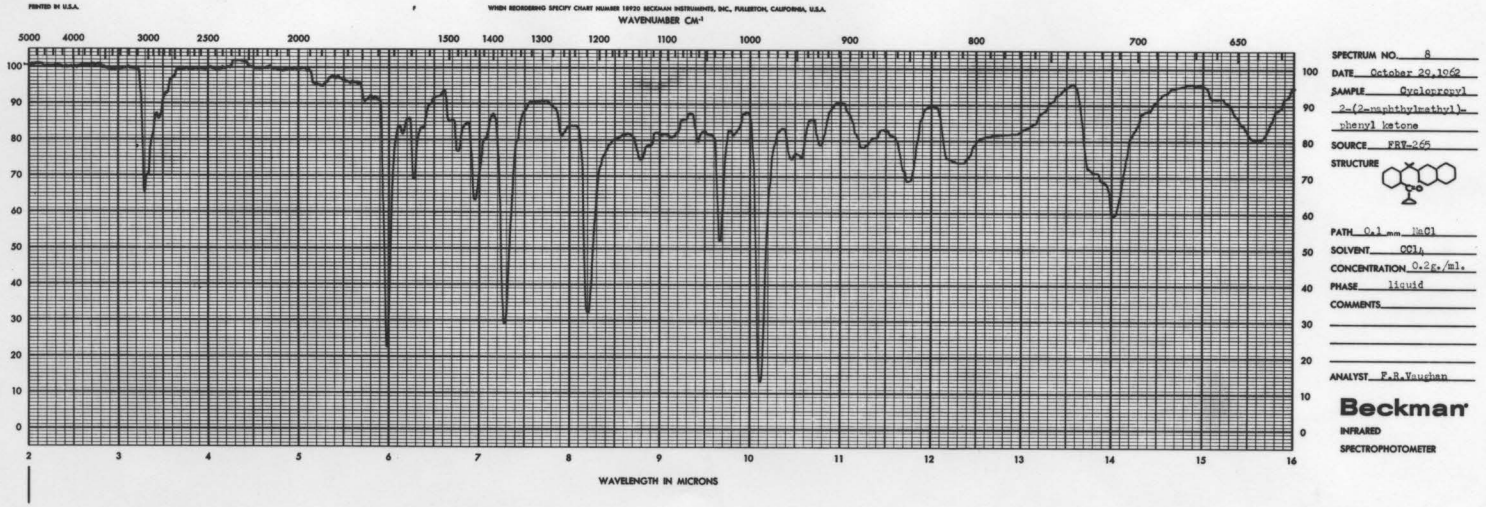
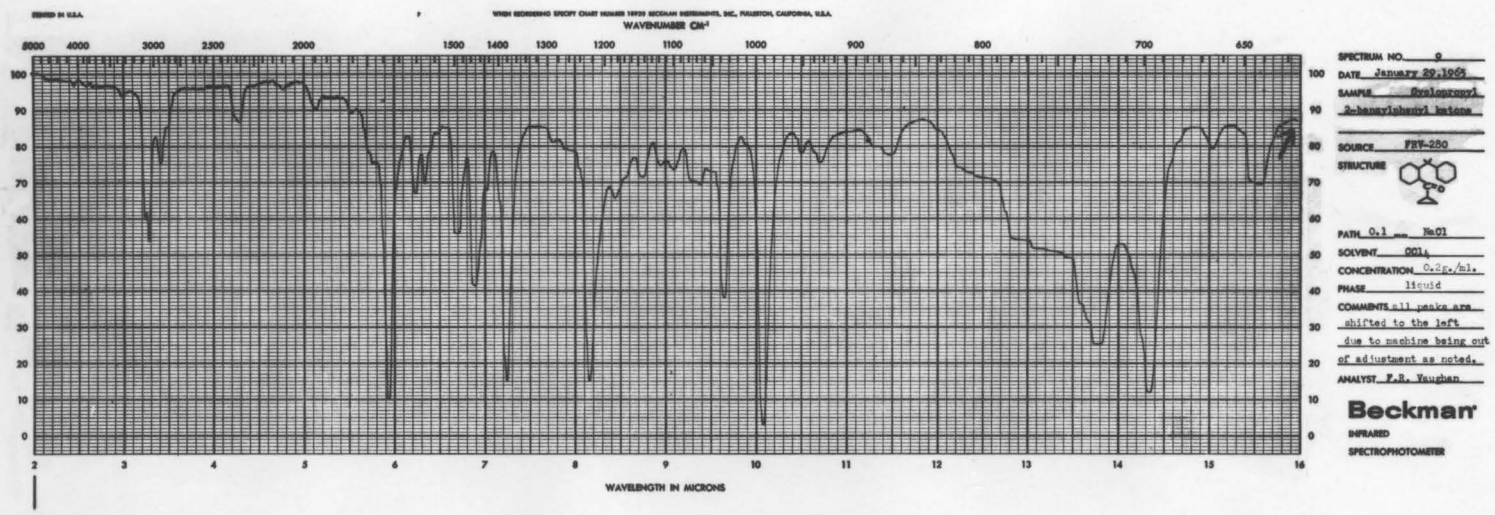
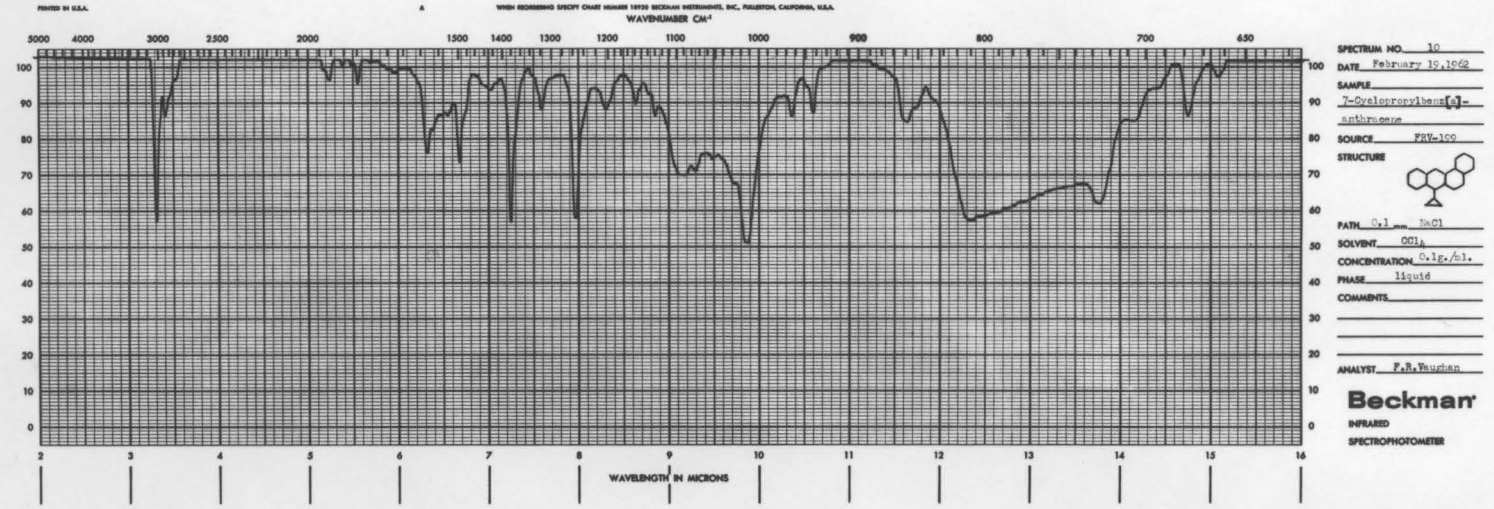
WHEN REORDERING SPECIFY CHART NUMBER 10920 BECKMAN INSTRUMENTS, INC., FULLERTON, CALIFORNIA, U.S.A.
WAVENUMBER CM-1
5000 4000 3000 2500 2000 1500 1400 1300 1200 1100 1000 900 800 700 650
100 90 80 70 60 50 40 30 20 10 0
2 3 4 5 6 7 8 9 10 11 12 13 14 15 16
WAVELENGTH IN MICRONS
SPECTRUM NO. 7
DATE October 31, 1962
SAMPLE Cyclopropyl 2-(1-naphthylmethyl)-phenyl ketone
SOURCE FRV-266
STRUCTURE
PATH 0.1 mm. NaCl
SOLVENT CCl4
CONCENTRATION 0.2g./ml.
PHASE liquid
COMMENTS
ANALYST F.R.Vaughan
Beckman
INFRARED
SPECTROPHOTOMETER


PRINTED IN U.S.A.
WHEN REORDERING SPECIFY CHART NUMBER 10920 BECKMAN INSTRUMENTS, INC., FULLERTON, CALIFORNIA, U.S.A.
WAVENUMBER CM-1
5000 4000 3000 2500 2000 1500 1400 1300 1200 1100 1000 900 800 700 650
100 90 80 70 60 50 40 30 20 10 0
2 3 4 5 6 7 8 9 10 11 12 13 14 15 16
WAVELENGTH IN MICRONS
SPECTRUM NO. 8
DATE October 29,1962
SAMPLE Cyclopropyl 2-(2-naphthylmethyl)-phenyl ketone
SOURCE FRV-265
STRUCTURE
PATH 0.1 mm. NaCl
SOLVENT CCl4
CONCENTRATION 0.2g./ml.
PHASE liquid
COMMENTS
ANALYST F.R.Vaughan
Beckman
INFRARED
SPECTROPHOTOMETER


WAVENUMBER CM-1
5000 4000 3000 2500 2000 1500 1400 1300 1200 1100 1000 900 800 700 650
100 90 80 70 60 50 40 30 20 10 0
2 3 4 5 6 7 8 9 10 11 12 13 14 15 16
WAVELENGTH IN MICRONS
SPECTRUM NO. 9
DATE January 29,1963
SAMPLE Cyclopropyl 2-benzylphenyl ketone
SOURCE FRV-250
STRUCTURE
PATH 0.1 mm. NaCl
SOLVENT CCl4
CONCENTRATION 0.2g./ml.
PHASE liquid
COMMENTS all peaks are shifted to the left due to machine being out of adjustment as noted.
ANALYST F.R. Vaughan
Beckman
INFRARED
SPECTROPHOTOMETER


WAVENUMBER CM-1
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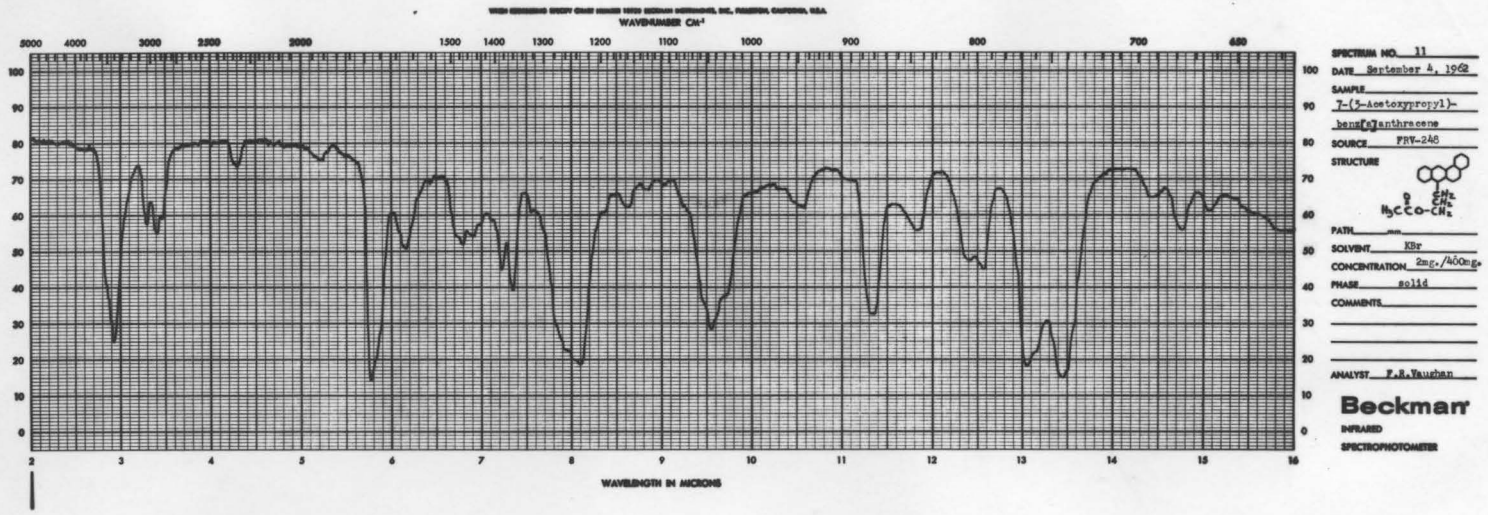
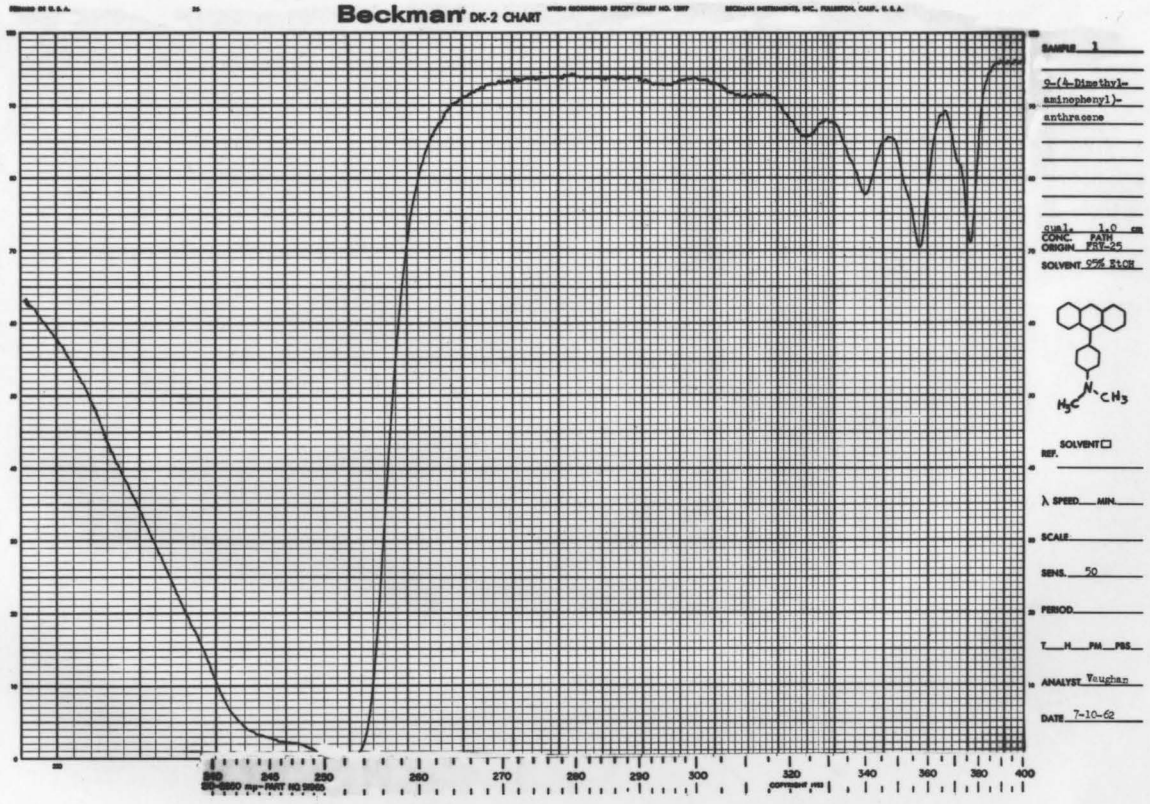
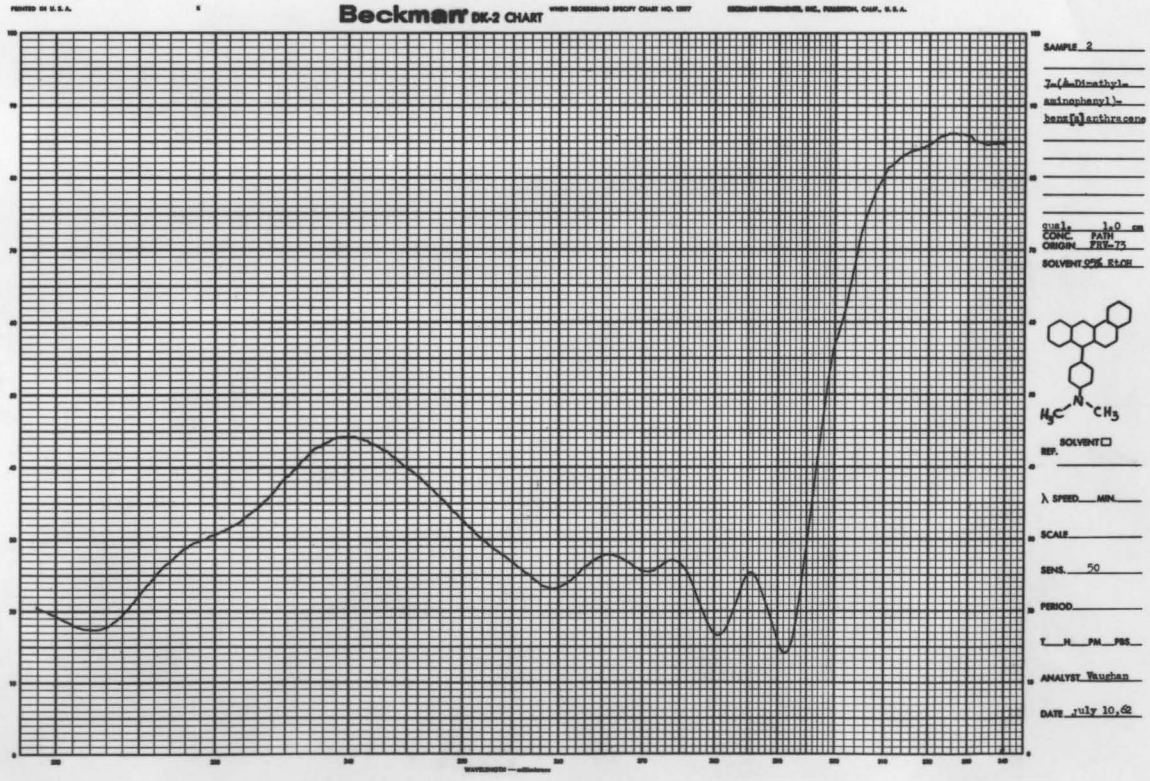
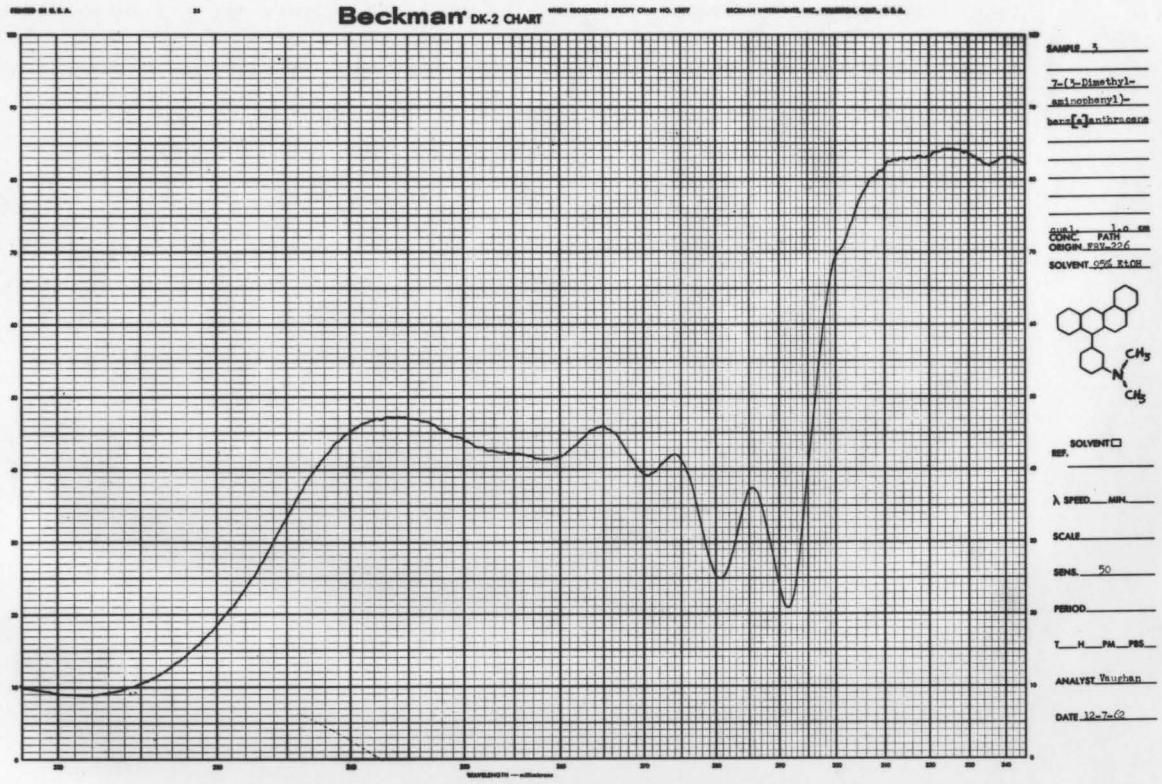
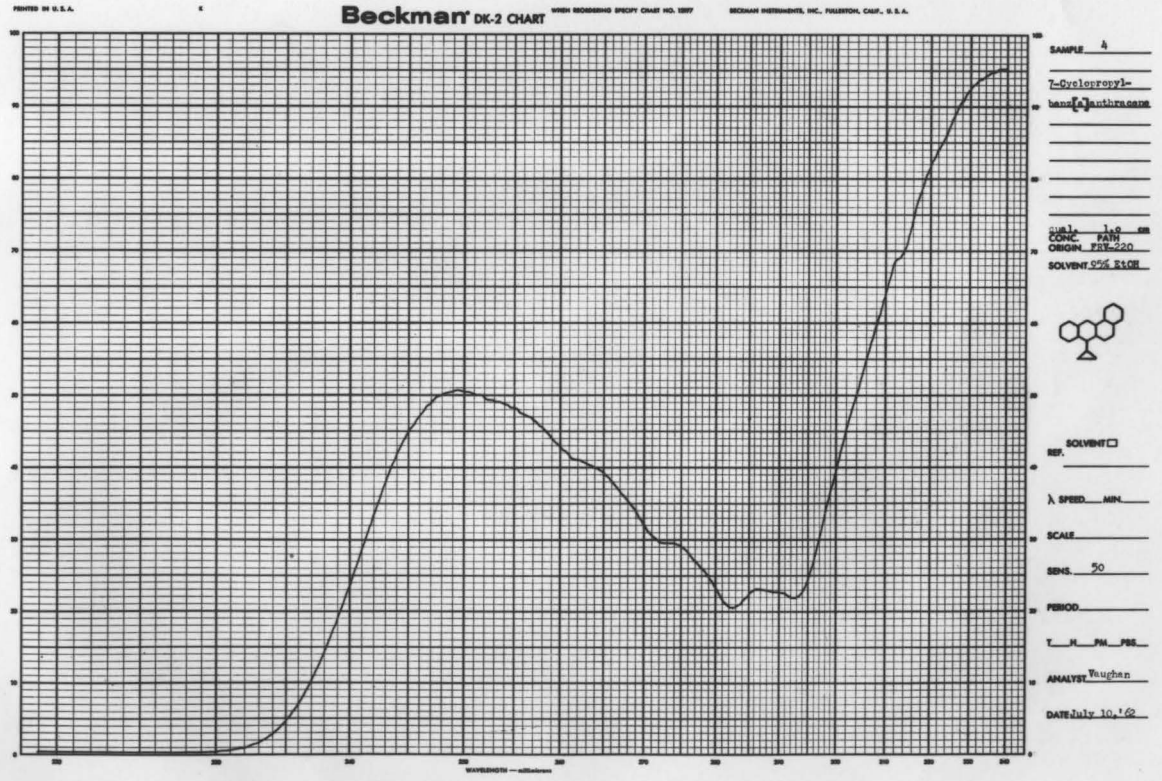
100 90 80 70 60 50 40 30 20 10 0
2 3 4 5 6 7 8 9 10 11 12 13 14 15 16
WAVELENGTH IN MICRONS
SPECTRUM NO. 10
DATE February 19,1962
SAMPLE 7-Cyclopropylbenz[a]-anthracene
SOURCE FRV-109
STRUCTURE
PATH 0.1 mm. NaCl
SOLVENT CCl4
CONCENTRATION 0.1g./ml.
PHASE liquid
COMMENTS
ANALYST F.R.Vaughan
Beckman
INFRARED
SPECTROPHOTOMETER

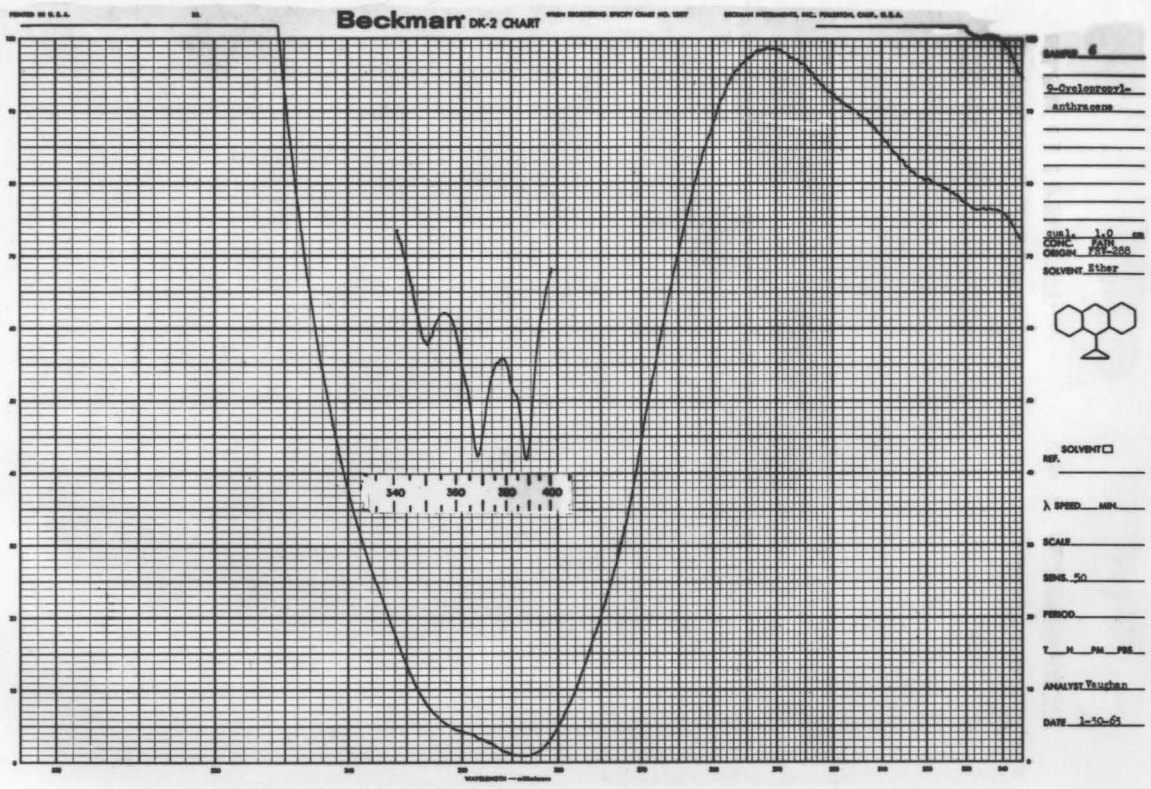

WAVENUMBER CM-1
5000 4000 3000 2500 2000 1500 1400 1300 1200 1100 1000 900 800 700 650
100 90 80 70 60 50 40 30 20 10 0
2 3 4 5 6 7 8 9 10 11 12 13 14 15 16
WAVELENGTH IN MICRONS
SPECTRUM NO. 11
DATE September 4, 1962
SAMPLE
7-(3-Acetoxypropyl)-
benz[a]anthracene
SOURCE FRY-246
STRUCTURE
PATH
SOLVENT KBr
CONCENTRATION 2mg./400mg.
PHASE solid
COMMENTS
ANALYST F.R.Vaughan
Beckman
INFRARED
SPECTROPHOTOMETER

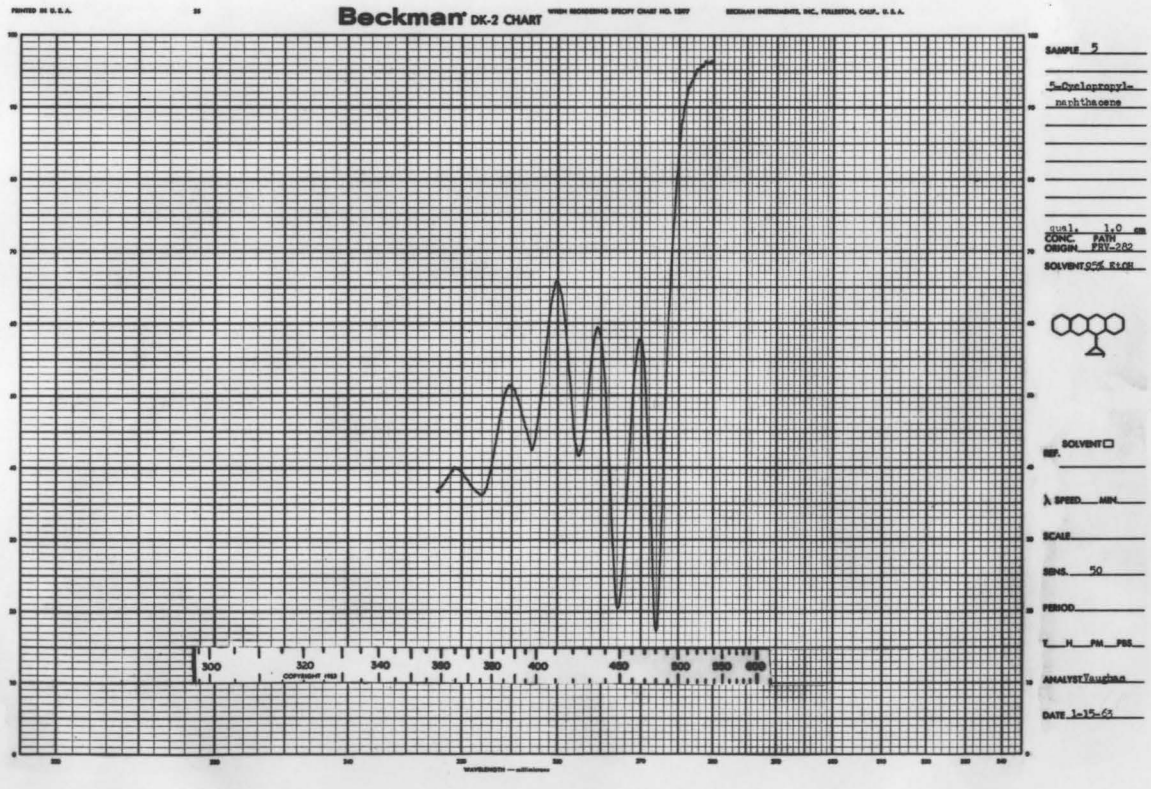

Beckman DK-2 CHART
SAMPLE 1
9-(4-Dimethyl-
aminophenyl)-
anthracene
qual.
CONC. PATH 1.0 cm
ORIGIN PRT-25
SOLVENT 95% EtOH
SOLVENT
REF.
λ SPEED MIN.
SCALE
SENS. 50
PERIOD
T H PM PBS
ANALYST Vaughan
DATE 7-10-62

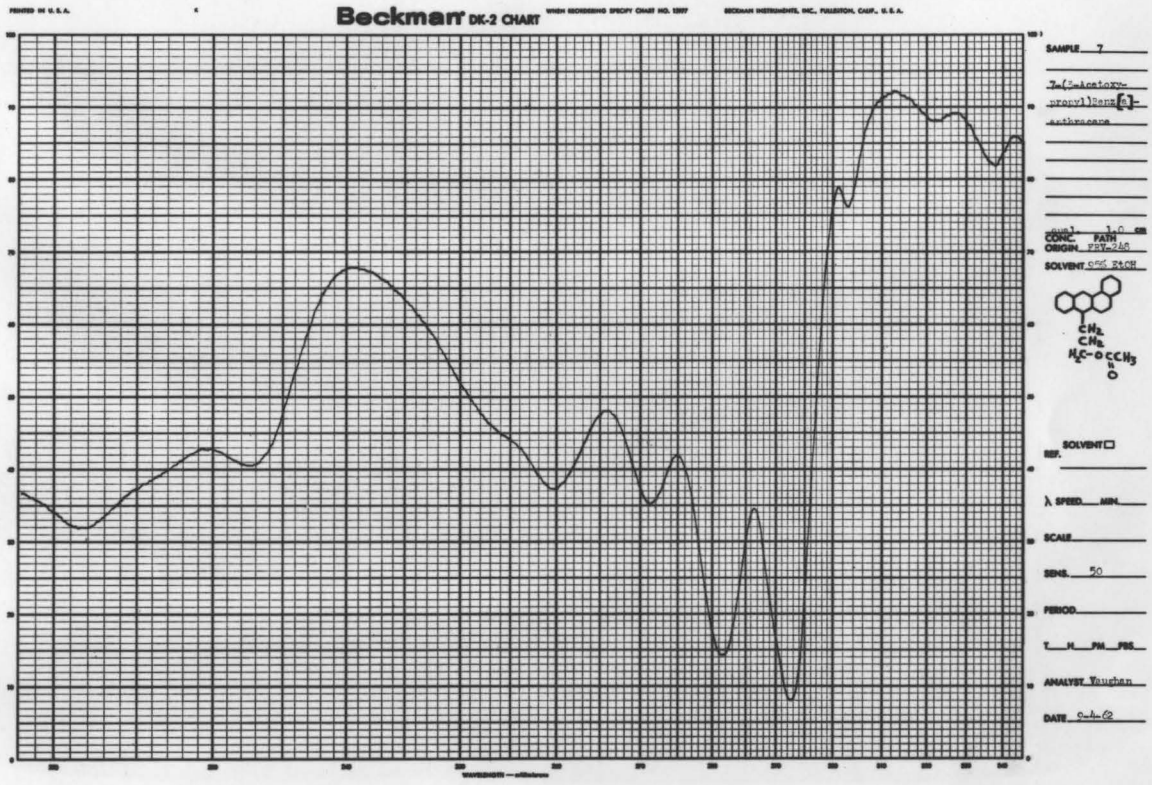

Beckman DK-2 CHART
SAMPLE 2
7-(4-Dimethyl-
aminophenyl)-
benz[a]anthracene
qual.
CONC. PATH 1.0 cm
ORIGIN PRT-75
SOLVENT 95% EtOH
SOLVENT
REF.
λ SPEED MIN.
SCALE
SENS. 50
PERIOD
T H PM PBS
ANALYST Vaughan
DATE July 10, 62


Beckman DK-2 CHART
SAMPLE 3
7-(3-Dimethyl-
aminophenyl)-
benz[a]anthracene
cuvl. 1.0 cm
CONC. PATH
ORIGIN PRT-226
SOLVENT 95% EtOH
SOLVENT
REF.
λ SPEED MIN.
SCALE
SENS. 50
PERIOD
T H PM PBS
ANALYST Vaughan
DATE 12-7-62
WAVELENGTH — millimicrons


Beckman DK-2 CHART
SAMPLE 4
7-Cyclopropyl-
benz[a]anthracene
cuvl. 1.0 cm
CONC. PATH
ORIGIN PRT-220
SOLVENT 95% EtOH
SOLVENT
REF.
λ SPEED MIN.
SCALE
SENS. 50
PERIOD
T H PM PBS
ANALYST Vaughan
DATE July 10, '62
WAVELENGTH — millimicrons


Beckman DK-2 CHART
SAMPLE 6
9-Cyclopropyl-
anthracene
qual. 1.0 cm
CONC. PATH
ORIGIN PRT-286
SOLVENT Ether
SOLVENT
REF.
λ SPEED MIN.
SCALE
SENS. 50
PERIOD
T H PM PBS
ANALYST Vaughan
DATE 1-30-65
340 360 380 400
WAVELENGTH — millimicrons


Beckman DK-2 CHART
SAMPLE 5
5-Cyclopropyl-
naphthacene
qual. 1.0 cm
CONC. PATH
ORIGIN PRT-282
SOLVENT 95% EtOH
SOLVENT
REF.
λ SPEED MIN.
SCALE
SENS. 50
PERIOD
T H PM PBS
ANALYST Vaughan
DATE 1-15-65
300 320 340 360 380 400 480 500 550 600
WAVELENGTH — millimicrons


Beckman DK-2 CHART
SAMPLE 7
7-(3-Acetoxy-propyl)Benz[a]-anthracene
CONC. PATH
ORIGIN PRV-2A8
SOLVENT 95% EtOH
SOLVENT
REF.
λ SPEED MIN.
SCALE
SENS. 50
PERIOD
ANALYST Vaughan
DATE 9-4-62

BIBLIOGRAPHY

BIBLIOGRAPHY

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ABSTRACT

The physiological activity of certain meso-substituted benz[a]anthracenes has been demonstrated by Cook and his co-workers. The powerful effect of the dimethylamino group on the carcinogenic activity of various compounds has been studied in detail. Since 7-phenylbenz[a]anthracene has demonstrated moderate carcinolytic properties, a logical extension in this field would be to test the effect of the three isomeric 7-dimethylaminophenylbenz[a]anthracenes.

The cyclopropane ring has been found infrequently in natural products but several instances of its presence in compounds being used clinically has prompted extensive testing of cyclopropyl derivatives. The structural similarity of the cyclopropane ring system to the powerful carcinolytes, substituted aziridines, suggests more strongly its possible value in chemotherapy.

The preparation of three new dimethylaminophenyl-benz[a]anthracenes, three new cyclopropyl substituted polycyclic compounds and one ring-opened propyl substituted polycyclic compound is discussed in detail. The compounds were characterized by elemental analysis

and by infrared and ultraviolet spectra. Four of these new compounds have been prepared in quantities sufficient for carcinolytic testing.

The cross-condensation reaction reported by Vingiello, Quo and Sheridan was employed successfully for the first time in the preparation of three frequently used intermediates.

Dimethylaminophenyl ketones were shown to cyclize quantitatively in very short reaction times. The theoretical explanation of this phenomenon, based on the electronic effects of the dimethylamino group, follows that which had been originally proposed by Bradsher and Vingiello. One of the dimethylaminophenyl derivatives was prepared by a base-catalyzed cyclization.

The unique electronic nature of the cyclopropyl group was discussed in some detail. When the attempted preparation of the cyclopropyl ketones passed through the ketimine intermediate, anomalous results were observed. An explanation for these anomalies was discussed fully. It was noted that during the reaction between 2-(1-naphthylmethyl)phenylmagnesium bromide and cyclopropyl cyanide cyclized material was formed. The reason for this phenomenon was discussed.

It was noted in the course of this study that all the usual methods of preparation failed in the synthesis of 12-cyclopropylbenz[a]anthracene. In two instances 5-cyclopropylnaphthacene was obtained instead. Steric and electronic explanations for this phenomenon were presented and discussed fully.

During the synthesis of the seven new polycyclic systems, seven new intermediates were prepared along with two rearrangement products. These other new compounds include six ketones, one nitrile and two pyrrolines. Infrared and/or ultraviolet spectra of the new compounds were recorded.

Suggestions for future work were presented.